

COUNTWAY LIBRARY



HC 175R Q



William B. Castle

Boston City Hospital

MANSON'S
TROPICAL DISEASES

MANSON'S TROPICAL DISEASES

A MANUAL OF THE DISEASES
OF WARM CLIMATES

EDITED BY

PHILIP H. MANSON-BAHR

D.S.O., M.A., M.D., D.T.M. AND H. CANTAB.,
F.R.C.P. LOND.

Physician to the Hospital for Tropical Diseases, London, the Albert Dock Hospital and the Tilbury Hospital; Lecturer at the London School of Hygiene and Tropical Medicine; Member Colonial Medical Research Committee; Lecturer on Tropical Diseases to the London Hospital, the West London Post Graduate College, and the North-Eastern Post Graduate College; Consultant in Tropical Medicine to the Royal Air Force; Corresponding Member of the Société de Pathologie Exotique; Examiner in Tropical Medicine to the Conjoint Board of the Royal College of Physicians and Royal College of Surgeons, England, and to Cambridge and Hongkong Universities.

Ninth Edition, Revised

WITH 23 COLOUR PLATES, 12 HALF-TONE PLATES,
401 FIGURES IN THE TEXT, 6 MAPS, AND 34 CHARTS

BOSTON MEDICAL LIBRARY
IN THE
FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE

NEW YORK
WILLIAM WOOD AND COMPANY
MDCCCXXXI

Printed in Great Britain

PREFACE TO THE NINTH EDITION

PROBABLY in no other department of medicine have advances, both in diagnosis and in treatment, been so many or so striking as in the practice of medicine in the tropics, and it may still be observed that the special methods evolved contribute materially to the furtherance of medical practice in general. This is particularly true of malaria, kala-azar, dysentery and sprue.

In this, the Ninth Edition, attention has been especially directed to the subject of treatment—now, happily, becoming more and more stabilized—in recognition of the paramount position that clinical study and clinical methods still hold in Tropical Medicine. In the present as in former editions, therefore, ancillary subjects such as Medical Zoology are appropriately treated, as fully as space will permit, in the Appendix.

While it has been the good fortune of the Editor to record many additions to knowledge in the present volume, it has been necessary in some subjects, such, for example, as yellow fever, to re-examine and remodel previously conceived ideas in the light of recent investigations. At the same time every effort has been made to keep the size of this volume well within the limits observed in former editions, and although three new coloured plates and five half-tone plates, as well as some thirty new text figures, have been incorporated, the total number of pages remains practically the same. In the Appendix, the proto-zoological and laboratory sections have been thoroughly revised and brought up to date. In short, every effort has been made

to bring the new edition up to present-day requirements; this revision has been possible, however, without altering the general arrangement of the subject matter.

The Editor wishes to express his thanks to Dr. C. M. Wenyon, F.R.S., for having undertaken the supervision of the protozoological section. He is indebted, as in the Eighth Edition, to Lieut.-Colonel W. P. MacArthur, D.S.O., for advice on zoological nomenclature, to Major E. E. Austen, D.S.O., for revising the section on Tsetse-flies, and to Dr. A. L. Gregg for his willing co-operation in a new section on the technique of blood transfusion suitable for employment in the tropics. Finally, he wishes to thank correspondents in many parts of the world for suggestions and corrections, to all of which due attention has been paid.

PHILIP MANSON-BAHR.

9, Weymouth Street, W.1.

December, 1928.

PREFACE TO THE FIRST EDITION

A MANUAL on the diseases of warm climates, of handy size, and yet giving adequate information, has long been a want; for the exigencies of travel and of tropical life are, as a rule, incompatible with big volumes and large libraries. This is the reason for the present work.

While it is hoped that the book may prove of practical service, it makes no pretension to being anything more than an introduction to the important department of medicine of which it treats; in no sense is it put forward as a complete treatise, or as being in this respect comparable to the more elaborate works by Davidson, Scheube, Rho, Laveran, Corre, Roux, and other systematic writers in the same field.

The author avails himself of this opportunity to acknowledge the valuable assistance he has received, in revising the text, from Dr. L. Westenra Sambon and Mr. David Rees, M.R.C.S., L.R.C.P., Superintendent, London School of Tropical Medicine. He would also acknowledge his great obligation to Mr. Richard Muir, Pathological Laboratory, Edinburgh University, for his care and skill in preparing the illustrations

CONTENTS

	PAGE
INTRODUCTION	XV

Section I.—Fevers

CHAPTER

1. MALARIA	1
2. MALARIA (<i>continued</i>) AND BLACKWATER FEVER . . .	44
3. HUMAN TRYPANOSOMIASIS	101
4. LEISHMANIASIS	132
5. DISEASES DUE TO BLOOD SPIROCHÆTES (<i>TREPONEMA</i>) .	164
6. DISEASES DUE TO BLOOD SPIROCHÆTES (<i>LEPTOSPIRA</i>) .	181
7. YELLOW FEVER	190
8. DENGUE AND PHLEBOTOMUS FEVER	205
9. RAT-BITE FEVER	215
10. TYPHUS AND ALLIED FEVERS	219
11. OROYA FEVER AND VERRUGA PERUANA	233
12. PLAGUE	239
13. TULARÆMIA AND MELIOIDOSIS	264
14. UNDULANT FEVER	269
15. FEVERS OF THE ENTERIC GROUP	282
16. THE SMALLPOX GROUP: ALASTRIM	299
17. HEAT-STROKE	302
18. THE DIAGNOSIS OF FEVERS IN THE TROPICS . . .	309

Section II.—General Diseases of Undetermined Nature

19. BERIBERI, EPIDEMIC DROPSY, AND CENTRAL NEURITIS	321
20. PELLAGRA	346
21. SCURVY IN THE TROPICS	358

Section III.—Abdominal Diseases

CHAPTER	PAGE
22. CHOLERA	362
23. THE DYSENTERIES	380
24. THE DYSENTERIES (<i>concluded</i>)	402
25. SPRUE	440
26. TROPICAL LIVER	461
27. INFANTILE BILIARY CIRRHOSIS	463

Section IV.—Infective Granulomatous Diseases

28. LEPROSY (ELEPHANTIASIS GRÆCORUM)	465
29. YAWS (FRAMBÆSIA)	486
30. ULCERATING GRANULOMA OF THE PUDENDA	505

Section V.—Animal Parasites and Associated Diseases

31. PARASITES OF THE CIRCULATORY SYSTEM : SCHISTOSOMIASIS	511
32. PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES : FILARIASIS	535
33. PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES : FILARIASIS (<i>concluded</i>)	569
34. PARASITES OF THE LUNG AND LIVER (PARAGONIMIASIS ; CLONORCHIASIS)	581
35. INTESTINAL PARASITES (ASCARIASIS ; ANCYLOSTOMIASIS ; CESTODES)	587

Section VI.—Diseases due to Poisons, including Snake-bite, and Infection with Dipterous Flies and Leeches

36. VEGETABLE POISONS	604
37. ANIMAL POISONS	609
38. MYIASIS AND LEECH INFECTION	617

Section VII.—Tropical Skin Diseases

39. NON-SPECIFIC, BACTERIAL, AND FUNGOUS DISEASES, ETC.	623
---	-----

Section VIII.—Local Diseases of Problematical Nature

CHAPTER	PAGE
40. CLIMATIC BUBO—RHINOSPORIDIOSIS—AINHUM—BIG HEEL	659

Section IX.—Technique

41. TECHNIQUE OF INJECTIONS IN THE TREATMENT OF	
TROPICAL DISEASES	664
INTRAVENOUS THERAPY	664
INTRAMUSCULAR INJECTIONS	666
INTRAVENOUS INJECTION OF SALINES	667
INTRAVENOUS TRANSFUSION OF BLOOD	668

APPENDIX

Section A.—Medical Zoology

1. INTRODUCTORY	670
2. MEDICAL PROTOZOOLOGY	672
SARCODINA	674
MASTIGOPHORA	680
SPOROZOA	696
INFUSORIA	706
SPIROCHÆTES	708
3. MEDICAL HELMINTHOLOGY	711
TREMATODA	711
CESTODA	739
NEMATODA	754
4. MEDICAL ENTOMOLOGY	792
ARACHNIDA	792
INSECTA	803
5. MEDICAL HERPETOLOGY	844
A SYNOPSIS OF THE VENOMOUS SNAKES	844
COLUBRIDÆ	847
VIPERIDÆ	853

*Appendix—continued***Section B.—Laboratory Methods**

	PAGE
1. CLEANING SLIDES AND COVER-SLIPS	857
2. METHODS OF PREPARATION OF BLOOD-FILMS	857
3. STAINING OF BLOOD-FILMS FOR PROTOZOA AND FOR THE DIFFERENTIAL COUNT OF CELLS	859
4. VARIETIES OF BLOOD-CELLS, AND THEIR SIGNIFICANCE .	861
5. ENUMERATION OF BLOOD-CELLS AND ESTIMATION OF HÆMOGLOBIN	863
6. PREPARATION OF SPECIAL CULTURE MEDIA	864
7. CULTIVATION OF ORGANISMS FROM THE BLOOD: EX- AMINATION OF CEREBRO-SPINAL FLUID	866
8. AGGLUTINATION WITH PATIENT'S SERUM FOR TYPHOID, PARATYPHOID, AND UNDULANT FEVER	868
9. RECOGNITION OF ORGANISMS BY AGGLUTINATION	874
10. CHEMICAL AND MICROSCOPICAL EXAMINATION OF FÆCES	874
11. SPECTROSCOPIC EXAMINATION OF URINE AND OTHER FLUIDS	882
12. DETECTION OF SPIROCHÆTES BY DARK-GROUND ILLUMINA- TION AND STAINING METHODS	883
13. METHODS OF PRESERVING HELMINTHS AND THEIR EGGS	885
14. METHODS OF REARING, DISSECTING, AND PRESERVING MOSQUITOES	886
15. SCALES AND STANDARDS	889
INDEX	891

LIST OF PLATES

	FACING PAGE
1. TWO MALARIA-CARRYING ANOPHELES (<i>colour</i>)	8
2. MALARIA PARASITES (<i>colour</i>)	24
3. THE BLOOD PICTURE IN QUARTAN AND MIXED INFEC- TIONS (<i>colour</i>)	26
4. MALARIA PARASITES (STAINED)	28
5. THE BLOOD PICTURE IN BENIGN TERTIAN MALARIA (<i>colour</i>)	30
6. THE BLOOD PICTURE IN SUBTERTIAN MALARIA (<i>colour</i>) .	32
7. SUBTERTIAN MALARIA (<i>colour</i>)	40
8. BLACKWATER-FEVER URINE (<i>colour</i>)	50
9. TSETSE-FLIES (<i>colour</i>)	104
10. LEISHMAN-DONOVAN BODIES IN KALA-AZAR (<i>colour</i>) .	134
11. TICKS (<i>colour</i>)	168
12. AÆDES (STEGOMYIA) ARGENTEUS (<i>colour</i>)	190
13. DENGUE RASH (<i>colour</i>)	208
14. APPEARANCE OF BRUCELLA ABORTUS AND BR. MELITENSIS ON CULTURE	272
15. ALASTRIM	300
16. PELLAGRA (<i>colour</i>)	354
17. PELLAGRA RASH ON FEET	356
18. INTESTINAL LESIONS IN AMŒBIC AND BACILLARY DYS- ENTERY (<i>colour</i>)	384
19. MICROSCOPICAL SECTION OF LARGE INTESTINE IN BACILLARY DYSENTERY	386
20. MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE IN ACUTE BACILLARY DYSENTERY (<i>colour</i>)	facing Plate 21
21. MICROSCOPIC APPEARANCE OF EXUDATE IN AMŒBIC DYSENTERY (<i>colour</i>)	390

22. SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACIL- LARY AND AMŒBIC DYSENTERY (<i>colour</i>) . . .	393
23. LIVER ABSCESS	422
24. LIVER ABSCESS (<i>radiograph</i>)	432
25. SPRUE TONGUES (<i>colour</i>)	444
26. EARLY MACULAR RASH OF LEPROSY (<i>colour</i>) . . .	470
27. ANÆSTHETIC LEPROSY	475
28. URINARY SCHISTOSOMIASIS (<i>radiograph</i>) . . .	516
29. SCHISTOSOMIASIS OF THE FAR EAST	532
30. MICROFILARIÆ OF THE BLOOD (<i>colour</i>)	535
31. AÆDES (STEGOMYIA) VARIEGATUS (<i>colour</i>) . . .	542
32. TINEA IMBRICATA	648
33. PINTA	650
FOLDING PLATE OF SYNOPSIS OF GENUS GLOSSINA . .	824
34. NORMAL AND ABNORMAL BLOOD-CELLS (<i>colour</i>) . .	860
35. EGGS OF THE MORE COMMON HELMINTHS FOUND IN MAN (<i>colour</i>)	874

LIST OF MAPS

MAP

1. DISTRIBUTION OF HUMAN TRYPANOSOMIASIS	100
2. EQUATORIAL AFRICA, SHOWING DISTRIBUTION OF AFRICAN SLEEPING SICKNESS. <i>Follows Map 1</i>	
3. DISTRIBUTION OF LEISHMANIASIS	132
4. DISTRIBUTION OF YELLOW FEVER	192
5. DISTRIBUTION OF SCHISTOSOMIASIS	512
6. DISTRIBUTION OF FILARIASIS	536

INTRODUCTION

The Etiology of Tropical Diseases

THE title which I have elected to give to this work, TROPICAL DISEASES, is more convenient than accurate. If by "tropical diseases" be meant diseases peculiar to the tropics, then half a dozen pages might have sufficed for their description; for, at most, only two or three comparatively unimportant diseases strictly deserve that title. If, on the other hand, the expression "tropical diseases" be held to include all diseases occurring in the tropics, then the work would require to cover almost the entire range of medicine; for the diseases of temperate climates are also, and in almost every instance, to be found in tropical climates.

I employ the term "tropical" in a meteorological rather than in a geographical sense, meaning by it sustained high atmospheric temperature; and by the term "tropical diseases" I wish to indicate diseases occurring only, or which from one circumstance or another are specially prevalent, in warm climates.

It must not be inferred from this, however, that high atmospheric temperature is the sole and direct cause of the bulk of tropical diseases. The physiological machinery of the human body is so adjusted that great variations of atmospheric temperature can be supported by man with impunity. Indeed, although temperature acts as an important pathogenic factor, it is very rarely that it does so directly. Extreme cold may cause frost-bite; exposure to the sun, sun erythema, sun headache, and symptomatic fever; a hot atmosphere, heat-exhaustion; prolonged residence in hot moist climates, vague, ill-defined conditions of debility; profuse sweating from heat of climate, prickly heat. But none of these states can with justice be regarded as disease.

This being so, it is natural to ask: In what way do tropical influences affect disease, as they undoubtedly do; and why should it be that some diseases are peculiar to tropical climates, or are specially prevalent in such climates?

Speaking generally, the natives of tropical countries are not injuriously affected by the meteorological conditions of the climates they live in, any more than are the inhabitants of more temperate

climates ; their physiological activities are attuned by heredity and habit to the conditions they were born into. The European, it may be, on his first entering the tropics, and until his machinery has adjusted itself to the altered meteorological circumstances, is liable to slight physiological irregularities, and this more especially if he persist in the dietetic habits appropriate to his native land. A predisposition to certain diseases, and a tendency to degenerative changes, may be brought about in this way ; but acute disease, with active tissue change, is not so caused. In the tropics, as in temperate climates, in the European and in the native alike, nearly all disease is of specific origin. It is in their specific causes that the difference between the diseases of temperate climates and those of tropical climates principally lies.

Modern science has clearly shown that nearly all diseases, directly or indirectly, are caused by germs. It must be confessed that although in many instances these germs have been discovered, in other instances they are yet to find ; nevertheless, their existence in the latter may be confidently postulated.

Germs are living organisms, and, like all living things, demand certain physical conditions for their well-being. One of these conditions is a certain temperature ; another is certain media ; and a third is certain opportunities.

In the majority of instances disease germs are true parasites, and therefore, to keep in existence as species, require to pass from host to host. If, during this passage from host to host the temperature of the transmitting medium—be it air, water, or food—be too high or too low for the special requirements of the germ in question, that germ dies and ceases to be infective. In this way may be explained the absence from the tropics of a class of directly infectious diseases represented by scarlet fever, and the possible absence from temperate climates of a similar class of diseases. In the one case, during the short passage from one human being to another, tropical temperature is fatal to the air-borne germ ; in the other it may be that the lower temperature of higher latitudes has the same effect.

In another type of disease, of which tropical scaly ringworm (*tinea imbricata*) is an excellent example, the germ vegetates on the surface of the body, and is thus exposed to the vicissitudes of climate. One of the requirements of the germ referred to is a high atmospheric temperature and a certain degree of moisture. Given these it flourishes ; remove these and it dies out, just as a palm tree or a bird of paradise would die on being transferred to a cold climate.

Many diseases require for their transmission from one individual to another the services of a third and wholly different animal. The propagation and continued existence of a disease of this description will depend, therefore, on the presence of the third animal. If the latter be a tropical species, the disease for the transmission of which it is indispensable must necessarily be confined to the tropics. Thus the geographical range of malaria and of filariasis is determined by that of certain species of mosquito which ingest and act as alternative hosts to the respective germs, and, so to speak, prepare them for entrance into their human host. The distribution of a large number of animal parasitic diseases depends in this way on the distribution of these alternative hosts. When this animal happens to be a tropical species, the disease it subtends, so to speak, is, in natural conditions, necessarily tropical also.

Certain diseases are common to man and the lower animals. If these latter happen to be tropical species, the opportunities for man to contract the common disease are most frequent, or are only found, in the tropics. Such, most probably, are some of the tropical ringworms.

Certain parasites are so organized that before re-entering man they must pass a part of their lives as free organisms in the outer world, where they require a relatively high temperature for their development. Such parasites, therefore, and the diseases they give rise to, must necessarily be tropical or subtropical. The *Ancylostoma duodenale* and ancylostomiasis are an instance in point.

There is a class of intoxication diseases which depend on toxins generated by germs whose habitat is the soil, water, or other external media, and whose germs do not enter the human body as a necessary feature in their life-histories, although their toxins may. The yeast plant and its toxin, alcohol, and the disease it causes, alcoholism, are the most familiar example of this. Such, too, are ergotism, atropicism, and perhaps lathyrism. These germs require certain temperatures and certain media; consequently the diseases they produce have a corresponding geographical range. If one of these conditions be a high temperature, the disease is mainly a tropical one.

Lastly, I can conceive, and believe, that there is another and less directly-acting set of conditions influencing the distribution of disease—conditions which as yet have been ignored by epidemiologists, but which, it seems to me, must have an important bearing on this subject. Disease germs, their transmitting agencies, or

their intermediate hosts, being living organisms, are, during their extracorporeal phases, necessarily competing organisms, and therefore liable to be preyed upon or otherwise crushed out by other organisms in the struggle for existence. The malaria parasite is absent in many places in which, apparently, all the conditions favourable to its existence are to be found in perfection. Why is it not found there, seeing that it must certainly have been frequently introduced? I would suggest that in some instances this and other disease germs, or the organisms subtending them, are kept under by natural enemies which prey on them, just as fishes prey on and keep down water-haunting insects, or as mice do humble-bees. The geographical range of such disease germs, therefore, will depend, not only on the presence of favourable conditions, but, also, on the absence of unfavourable ones. Herein lies a vast field for study, and one which, as yet, has not been touched by epidemiologists.

In these and similar ways the peculiar distribution of tropical diseases is regulated. The more we learn about these diseases the less important in its bearing on their geographical distribution, and as a direct pathogenic agency, becomes the rôle of temperature *per se*, and the more important the influence of the tropical fauna.

Whatever may have been the original source of the pathogenic parasites of man, it is certain that many of those which have a wide distribution at the present day were much more restricted originally. The extension of many of them has occurred within historical, and of some even in recent, times. Thus, in the last century, cholera spread over a great part of the world from its reputed home in India. Smallpox and other Old-World diseases have crossed the Atlantic; and some originally American diseases, such as syphilis and the chigger, have appeared in the Old World; measles, whooping-cough, tuberculosis, and leprosy have been introduced into the Pacific islands. The process of diffusion is still proceeding, assisted, doubtless, by the vastly increased rapidity and frequency of modern travel, and by the breaking down in recent times of social, political, and physical barriers that formerly isolated many communities, some of which had been from time immemorial the sole repositories of particular disease germs. Thus the sleeping sickness of West Africa is passing to East Africa, and thus, most probably, the yellow fever of America will pass to Asia.

There is one factor which undoubtedly has contributed powerfully to delay the diffusion of certain tropical diseases—the circumstance that most of them depend on protozoal or some other kind

of animal germ requiring for its transmission an animal intermediary. Diseases which depend on bacterial germs, if their special bacterium be introduced, social and sanitary conditions being favourable, will spread in any country or climate, and thus it is that all bacterial diseases, with hardly an exception, are found, or are capable of existing, everywhere; in the passage from host to host their germs are not killed by ordinary atmospheric conditions, and they require no second intermediary. Diseases depending on protozoa or other animal germs, in many though not in all instances, will not establish themselves thus universally, because their germs in the passage from host to host demand, through their intermediaries or otherwise, very special and climatically restricted conditions. Tropical diseases belong for the most part to this category, and therefore their successful introduction and spread to new ground are attended with more difficulty than bacterial diseases, demanding, as the former generally do, the double condition of the successful introduction, not only of the germ itself, but also of the intermediary.

Although this double necessity has undoubtedly operated powerfully against the spread of certain tropical diseases, there is reason to believe that in time this difficulty will disappear; for, so far as we know, there is no reason why, if introduced into new places, these animal intermediaries should not obtain a permanent footing and spread.

There are many instances of exotic insects, for example, which have established themselves after either accidental or intentional introduction into new countries. There is no reason, therefore, for thinking that disease-germ insect intermediaries could not be similarly established in countries in which they are unknown at present. Thus, if the tsetse-flies were successfully introduced into India, sleeping sickness might appear there in due course, or, if appropriate anopheles were introduced into many at present malaria-free and salubrious Pacific islands, malaria would become established there. And thus, though certain tropical diseases have at present a limited range, there is great probability, unless measures are speedily set on foot to prevent such a calamity, that the swift and increasing intercourse of modern times, by facilitating the intentional or accidental introduction of their subserving intermediaries, will ere long enable them to extend their present geographical range.

It is evident from what has been advanced that the student of medicine must be a naturalist before he can hope to become a scientific epidemiologist, or pathologist, or a capable practitioner. The necessity for this in all departments of medicine is yearly

becoming more apparent, but especially so in that section of medicine which relates to tropical disease. This is further accentuated if we reflect that, although we do know something about a few of the tropical diseases and their germs, there must be many more tropical diseases and tropical disease germs about which we know absolutely nothing. Who can doubt that just as the fauna and flora of the tropical world are infinitely richer in species than those of colder climates, so there is a corresponding distribution in the wealth and poverty of pathogenic organisms; and that many, if not most, of the tropical diseases have yet to be differentiated? The discoveries of the last few years show this. Opportunities and appliances for original pathological study are, from circumstances, too often wanting to the tropical practitioner; but in this matter of the etiology of disease he certainly enjoys opportunities for original research and discovery far superior in novelty and interest to those at the command of his fellow-inquirer in the well-worked field of European and American research.

In the following pages I have included certain cosmopolitan diseases, such as leprosy, plague, and beri-beri, diseases which, properly speaking, do not depend in any very special way, or necessarily, on climatic conditions. They have been practically ousted from Europe and the temperate parts of America by the spread of civilization and the improved hygiene that has followed in its train. They are now virtually confined to tropical and sub-tropical countries, where they still survive under those backward social and sanitary conditions which are necessary for their successful propagation, and which are more or less an indirect outcome of tropical climate.

PATRICK MANSON.

TROPICAL DISEASES

Section I.—FEVERS

CHAPTER I

MALARIA

Definition.—The term malaria is applied to certain fevers which are produced by protozoan parasites belonging zoologically to the class Sporozoa. These parasites are peculiar to man, who constitutes their intermediary host, and in whose red blood-corpuscles they live and multiply, and may give rise to a periodic fever associated with anæmia, enlargement of the spleen, and the deposit of black pigment in that organ and elsewhere. As a rule the disease is amenable to quinine.

History.—Hippocrates appears to have already recognized periodic malarial fevers in the 5th century B.C. The introduction of cinchona in 1640 enabled clinicians, under the leadership of Morton, Torti and Sydenham, to separate malaria from other fevers. The next important step was the discovery by Meckel of the characteristic pigmentation of the viscera, in 1847; later, the presence of pigment in the peripheral blood was noted by Virchow and Planer. The parasite of malaria was definitely recognized by Laveran in 1880. He observed, for the first time, the eruption of long motile filaments (flagella) from the pigmented cells (crescents) which, on account of their immotility, had up to that time been regarded as inanimate objects. His observations were soon extended by Italian observers, among whom may be mentioned Marchiafava, Celli, Golgi, Bignami, and Bastianelli, but there was considerable divergence of opinion about the true meaning of this curious eruption of flagella, which was regarded by some as representing the dying stages of the parasite. Manson, having observed that the "flagellation" took place, not in the circulating blood, but after its withdrawal from the body, concluded that it represented the first step in its extracorporeal life. Arguing from the analogy of other blood parasites, and from ascertained epidemiological facts, he conjectured that certain species of mosquito removed the parasite from the human body, and that they constituted the medium in which biological changes necessary to fit the parasite for entrance into the human host took place.

Manson's hypothesis was definitely established for an analogous sporozoon disease of birds (*Plasmodium præcox*) by Ross, on the lines which the former had suggested. The latter showed that the mosquito not only removed

parasites from the bird, but also implanted them into new hosts. Grassi and his collaborators extended these observations to human malaria and demonstrated its carriage by anopheles mosquitoes. These observations were in harmony with the earlier view that malaria was associated with mosquitoes, and with the well-known fact of its prevalence in marshy districts. The natives of Central Africa, it is said, applied the same term to the mosquito as they did to malaria, while Emin Pasha¹ appreciated the protection that a mosquito-net afforded against the disease. Robert Koch appears to have conjectured that the infection could be carried by the bite of a blood-sucking insect; but the most accurate prediction as to the changes which would be found to take place in the malarial parasite during its sojourn outside the human body, and the mode of its transmission, was made by Richard Pfeiffer in 1892, in a paper in which he compares the hypothetical stages of the malarial parasites with those which he had worked out in the coccidium of the rabbit. King and Laveran appear to have expressed somewhat similar views about the mosquito-malarial theory as explaining the epidemiological facts of malaria.

The hypothesis of Manson and the work of Ross and Grassi definitely removed the subject from the realm of theory to that of actual fact. In 1894 and 1896 Manson² stated that the parasite of malaria must pass from host to host in order to survive; in other words, it must at the same time have an extracorporeal life. From the fact that the flagellated body does not develop until the blood containing the stage of the parasite known as the crescent has left the blood-vessels, he concluded, as we have seen, that the function, till then unknown, of the flagellum lay outside the human body, and that the flagellated body represented the first stage of the extracorporeal life of the malaria parasite. He further argued that, as the parasite in the blood is always enclosed in a red blood-corpuscle, it is incapable of leaving the body by its own efforts, since it is never passed in the excreta; he therefore suggested some blood-sucking insect as the medium of its removal from the circulation. This he believed to be the mosquito, since it is commonly present in malarial districts, and because its habits seemed to be well adapted for such a purpose. Further, basing his argument on what he had shown to occur in the case of *Filaria bancrofti*, and on the peculiarities of the distribution of malaria, he reasoned that only one particular species of mosquito would be capable of acting as the definitive host of the malaria parasite.

Ross's observations.—In 1895 Ross, in India, demonstrated that when blood-containing crescents are ingested by a mosquito, a large proportion of them proceed to flagellate, i.e. to the emission of flagella, now known to be microgametes. After most patient researches he demonstrated, in 1897, that in certain dappled-winged mosquitoes fed on cases of malaria, living and growing malaria parasites containing the characteristic pigment, hæmoglobin, were found in the stomach-wall. Early in the following year he proved that if a particular species of mosquito (*Culex*) be fed on the blood of birds containing a parasite—*Plasmodium præcox*—nearly allied to that of man, the parasite enters the stomach-wall of the insect, grows and sporulates there, with the production of *sporozoites* that subsequently enter the salivary gland of the insect, which is then capable of infecting other birds by its

¹ H M Stanley, "In Darkest Africa," 2nd Ed., 1890, ii. 30.

² *Brit. Med. Journ.*, Dec. 8, 1894; Goulstonian Lectures, *Brit. Med. Journ.*, March 14, 21, and 28, 1896.

bite. There was one gap in Ross's observations, which was filled by MacCallum, who showed in 1897 by observations on *Halteridium* and crescents that the function of the filament or flagellum after it breaks away from the parent sphere is to impregnate certain other granular spheres, which were originally crescent-shaped bodies, when floating in the blood-stream (see Fig. 10).

After impregnation, the latter are transformed into sharp-pointed travelling *vermicules*. By virtue of its locomotive properties the travelling vermicle of the malaria and allied parasites is enabled to lodge itself, where Ross first found it, in the stomach-wall of the mosquito.

Finally, on behalf of the Colonial Office and the London School of Tropical Medicine, Manson instituted two experiments which disposed for good and all of any objections that might have been advanced against the theory. Drs. Sambon and Low, Mr. Terzi, their servants and visitors, lived for the three most malarial months of 1900 in one of the most heavily infected localities of the Roman Campagna—Ostia—in a hut from which mosquitoes were excluded by a simple arrangement of wire gauze on the doors and windows. They moved freely about in the neighbourhood during the day, exposed themselves in all weathers, drank the water of the place, often did hard manual work, and, beyond retiring from sunset to sunrise to their mosquito-protected hut, observed no precautions whatever against malaria. They took no quinine. Although their neighbours, the Italian peasants, were each and all of them attacked with malaria, the dwellers in the mosquito-proof hut enjoyed an absolute immunity from the disease. While this experiment was in progress, mosquitoes fed in Rome on patients suffering from tertian malaria were forwarded in suitable cages to the London School of Tropical Medicine, and on their arrival were set to bite the late Dr. P. Thurburn Manson and Mr. George Warren. Shortly afterwards both of these gentlemen, neither of whom had been abroad or otherwise exposed to malarial influences, developed characteristic malarial fever, and malarial parasites were found in abundance in their blood, both at that time and on the occurrence of the several relapses of malarial fever from which they subsequently suffered.

The mosquito-malaria theory thus passed from the region of conjecture into that of fact.¹

Geographical distribution.—An adequate comprehension of the distribution of malaria entails a knowledge of the three different parasites which cause this disease and the associated fevers. The parasites of malaria are known as the *benign tertian*, the *quartan*, and the *subtertian*.

Benign tertian malaria.—The parasite which causes this fever has a distribution that extends far beyond the tropics and subtropics, although at the present day it is found most abundantly in warm countries. Its most northerly range is 60° N., for indigenous malaria has been recorded from Lake Ladoga in Russia and from Southern Sweden. It is known that in recent historical times severe epidemics have occurred in Denmark and Northern Germany,

¹ For further details of the interesting history of this subject the reader is referred to "The Life and Work of Sir Patrick Manson," Cassell & Co., 1927.

while under the name of ague or "marsh" fever it still occurs to a very limited extent in Southern England. In America it is prevalent in the valley of the Sacramento at 40° N.

The southern geographical extension is more limited. It occurs, though rarely, in southern Queensland at 20° S., and in Natal at 30° S. In South America it extends down to 40° S., that is, to the southern limits of Argentina.

As regards the altitude, this form of malaria has been recorded from Quito in the Andes at 9,000 feet, but in India it is seldom, if ever, met with above 6,000 feet. In the tropics themselves it is widespread, but there are certain malaria-free islands which are of great epidemiological interest. These are Barbados¹ in the Atlantic, Tahiti, Hawaii, Fiji, Samoa, and other Pacific islands which are situated at some considerable distance from the mainland, and where it is known that the anopheles mosquito does not occur; there are, of course, other groups, such as the Solomons and New Hebrides, situated in close proximity, where this mosquito abounds, and malaria is rife. Until comparatively recently, Mauritius and Réunion in the Indian Ocean were also malaria-free, but they are now fever-ridden owing to the introduction of anopheles from Madagascar. As a rule, infections of benign tertian malaria, in warm countries where seasonal variations of temperature occur, take place in the early spring or summer, due probably, as Wenyon points out, to the fact that the gametocytes of this parasite can lie latent in the blood of infected persons during the winter months.

Quartan malaria.—As compared with the other forms of malaria, quartan is comparatively rare. Until recently, it appears to have been commoner in temperate latitudes than in the tropics. It has been noted in Central Europe, but in the tropics themselves it is quite unknown in some highly malarious places. It has a peculiar patchy distribution in the Mediterranean area, in Macedonia, Palestine, Iraq, Southern India, and the Andaman Islands, and is the dominant form in certain districts of Ceylon and the Malay States. It occurs in New Guinea and adjacent islands. In Africa it is found sparingly in the central tropical belt from Kenya Colony to Sierra Leone. In the New World it is relatively rare in the West India Islands, though common in Antigua. It is found in Panama and Brazil.

The general statement that quartan fever is more a disease of

¹ Unfortunately malaria broke out in this island in the autumn of 1927 through the introduction of *Anopheles albimanus* which soon became established in suitable pools.

the temperate zone than of the true tropics, but that in both it has a very limited topographical distribution, probably expresses the truth.

In Macedonia, and in the regions south-west of the Caspian, the maximum incidence of quartan malaria occurs during the months July to September; but it was noted during the Great War that the infection remained almost entirely confined to the children of the native villages and did not spread to the troops, who were quartered in the vicinity for over three years. This is a feature of the quartan parasite which requires further investigation.

Subtertian malaria is confined to the warmer regions of the earth, and to the more intensely malarial districts in these; hence the name "tropical" which has been applied to this type of infection. Its limits correspond to a mean summer isotherm of 70° F., and a mean winter isotherm of 48° F. In Europe it is therefore rare, except in such highly malarious centres as Salonica and the Danube marshes; but in the tropics, wherever fever is popularly regarded as being peculiarly virulent, the subtertian parasite is common. Like the quartan parasite, it has a patchy distribution, especially in hot, dry, desert countries with a limited water supply. In the oases of northern Africa it is the commonest form met with. The same may be said of West Africa, Asia Minor, and in fact the greater part of the tropics. Recently subtertian malaria has been imported into Central Russia by refugees from Turkestan, and has spread as far north as Moscow, where fresh cases occur even in the winter season.

In the subtropical zones it only occurs as a primary infection in late summer or early autumn; hence the synonym *æstivo-autumnal fever* sometimes applied to it. This peculiarity, as regards seasonal and geographical distribution, may be explained by the fact that, for its development in the mosquito, the subtertian parasite is said to require a higher atmospheric temperature than suffices for the quartan and tertian parasites. Hence, although the benign and the subtertian parasites are generally found associated together, and the latter can be acquired at any time in the tropics, it is only in the summer or autumn that it can be acquired in the subtropics and more temperate zones. It is stated that if the atmospheric temperature falls below 15° C., the development of the oöcyst in the mosquito is arrested. On the other hand, when once the sporozoites have entered the salivary glands of the anopheles, they are capable of infecting man with the parasite, even during the winter season.

Epidemiology and endemiology of malaria.—In considering the epidemiology of malaria, two things must be carefully distinguished: (1) The circumstances leading to the invasion of the human body by the malaria parasite; (2) the circumstances favouring the clinical manifestation of such invasion.

(1) *Circumstances leading to the invasion of the human body by the malaria parasite.*—In the mosquito-malaria theory, now thoroughly established, we have the key to this problem. Whatever favours the presence and increase of the malaria-bearing species of mosquito tends to the increase of malaria, and vice versa; whatever favours the access of these insects, and the parasites which have passed into them, to the human body favours the acquisition of malaria.

The strip of flat, waterlogged country lying along the foot of mountain ranges, the deltas of large rivers, the pool-dotted beds of dried-up streams, areas of country which have fallen out of cultivation, recently deforested lands, are, in many instances, notoriously malarial. Well-drained uplands and carefully cultivated districts are, as a rule, healthy. There are, nevertheless, instances of elevated, arid, and sandy plains which, under certain hydraulic conditions, are intensely malarial. Towns, as a rule, are much less malarial than villages or the open country.

From time to time malaria extends beyond its endemic foci, spreading in epidemic form over large tracts of what is usually healthy country. There are a few well-authenticated instances of countries which, although previously exempt, subsequently became endemically malarial; and there are many instances of countries previously malarial which afterwards, especially under the influence of cultivation and drainage, became salubrious.

These circumstances evidently have reference to the distribution of species of malarial mosquitoes. Like other insects, mosquitoes occasionally, under specially favourable conditions, increase enormously in numbers and spread out in every direction. New species, which may belong to the malaria-bearing kinds, may be introduced into places where they formerly did not exist. Thus it is believed that a mosquito capable of subserving the malaria parasite was introduced in this way in the early 'sixties into Mauritius, an island whose fauna and flora had been hitherto very peculiar and special.

Wenyon explains the seasonal variations of the two dominant forms of malaria as observed in Macedonia and Palestine by the fact that the benign tertian type of infection tends to relapse over a long period and is more resistant to quinine, while in the subtertian,

though the individual attack may be more severe, the cases are more amenable to quinine treatment and there is little tendency for the infections to persist from one season to the next. At the height of the malaria season the numbers of benign and subtertian cases may be approximately equal, but the latter develops much more rapidly into a heavy infection and produces in a shorter time a greater number of gametocytes. Thus subtertian malaria tends to spread in epidemic form with greater rapidity, which is characteristic of these autumn epidemics, at a time when conditions are favourable. There is no evidence that any special species of anopheline mosquito is especially associated with one type of malaria.

Very remarkable is the circumstance that there are villages and districts in India, as pointed out by Christophers and Stephens, and similar districts in Italy, as pointed out by Celli, in which, though surrounded by highly malarious country and though anophelines abound, there is no malaria. The explanation of this anomaly is not apparent. Perhaps in these places there is some local substance on which the mosquitoes feed that is fatal to the parasite.

One of the most important conditions necessary to the sporogonic phase (p. 700) of the malaria parasite is a sustained average temperature of at least 60° F., and a humidity of at least 63 per cent. (Gill). The malaria parasite will not develop in the mosquito at low temperatures, but, when once infected, the anopheles is capable of conveying the disease to another individual at very low temperatures indeed. Altitude *per se* has, apparently, no influence on malaria. It is the decrease in temperature, usually implied by an increase in altitude, that is the real determining circumstance in bringing about a diminution in the prevalence of malaria in uplands. In the tropics an elevation of six or seven thousand feet may not secure immunity from malaria unless there be, at the same time, a corresponding and sufficient lowering of temperature.

Another important condition for the production of malaria is the presence of water. The mosquito thrives best in sluggish streams with grassy banks and many backwaters; still better, in small pools or other collections of water, as in broken bottles, empty tins, etc., where there are no fish to prey on the larvæ, and where the surface is not agitated by winds. One such puddle near a house may suffice to render that house unhealthy. As a general rule, the anophelines will not breed in foul or muddy water. Clear pools, as found in many desert oases, with a plentiful supply of green algæ, are their favourite haunts.

It is doubtful whether the malarial mosquito can be transported very far from its native pool. Generally speaking, some thousand or fifteen hundred yards of water between a ship and a malarious coast may suffice to secure immunity to the crew. About three miles on land from a malarial source is probably as effective. The diffusion of malaria by winds is generally extremely restricted. Inside a city may be quite healthy, while outside the walls the country may be pestilential. One village may be sickly, whilst a neighbouring village may be healthy. The intervention of a belt of trees between a malarial swamp and a village is said to protect from malaria the houses on the leeward side of the trees. The trees may filter out the mosquitoes by affording them protection from winds. Open windows and doors, by giving access to mosquitoes, are sources of danger in malarious countries; for this and similar reasons, sleeping on the ground, on the ground floor, or unprotected by a mosquito-curtain, is dangerous.

Evidently in conformity with the habits of the mosquito, the time just before sunrise and just after sunset, and the night, have the reputation of being the most dangerous as regards liability to contract the infection. Although mosquitoes are most active during twilight and night, they bite readily enough during the daytime in shady and windless places, as in thick jungle or in a dark room. A very few species are diurnal in habit. (Plate I.)

It has often been observed that in malarious countries, so long as the soil remains undisturbed, agues and the severer forms of fever are comparatively rare; but so soon as building, road-making, and other operations implying soil disturbance commence, then severe malarial fevers appear. Soil disturbance usually implies the formation of holes; holes imply puddles, and puddles imply mosquitoes. Earth-cutting, in the clearing of jungles, also induces changes in the general physical appearances of the locality, and thus may be introduced conditions favouring a species of mosquito hitherto unrepresented. The amount of malaria in a district is not always proportional to the number of anophelines in the locality.

(2) *Circumstances favouring the clinical manifestation of malarial invasion.*—As a rule, a successful malarial infection declares itself within a week or ten days. As with other infections, certain individuals resist the pathogenic influences of the malaria parasite for a longer period. A very few appear to be permanently immune. Everything tending to cause physiological depression favours susceptibility and acute manifestations.

A malarial subject, while in the mild climate of the tropics, may



Anopheles fumus Giles
India.

Anopheles maculatus Theobald,
Malaya

TWO MALARIA-CARRYING ANOPIELES. > 14
PLATE I

keep in fair health; but when he is plunged into the stormy winter of the North, is exposed to cold, and has long watches and fatiguing work, very probably latent malaria will become active and ague follow.

An introduction to the study of mosquitoes will be found on p. 804.

Immunity.—It is well known that the negro in Africa, although he does get fever, does not get it so frequently or so severely as the European, in spite of the fact that the latter, from his hygienic ways of living, is of the two much the less exposed to infection. It has been shown that the natives of malarious districts acquire their immunity from repeated and persistent infection in childhood. In such places the blood of practically every child up to three or four years of age contains malaria parasites. The proportion of infected children gradually becomes smaller with each additional year until adolescence is approached, when the blood becomes practically parasite-free and immunity is established.

The mortality from malaria is very great in native children; but it would appear that a relative tolerance is soon acquired, for although the negro child may have a rich infection of parasites in his blood, he may exhibit, perhaps in consequence partly of increasing immunity, partly of some racial and inherited quality, a remarkable tolerance of the malaria toxins. It has often been remarked that these dark-skinned children, with enormous spleens and a rich stock of malaria parasites in the blood, run about fever-free, and apparently in robust health. It is also a common experience that Europeans suffer more severely from the effects of their first infection of malaria, especially the subtertian form, than from subsequent attacks. There are certain individuals who, having acquired malaria in their youth, become afterwards wholly immune. Some of these observations have been made in the process of inoculating general paralysis with malaria. The Editor has observed one instance in which it was impossible to convey malarial infection, either by mosquito-bite or by direct blood inoculation, to an individual who had lived many years in India, and who had suffered much from malaria in his youth. The experimental production of immunity has been performed by Mühlens and Kirschbaum, who have shown that in human beings who are susceptible to two or even three artificial malaria inoculations, the infections are of decreasing intensity, while workers in the Dutch East Indies have shown that some natives are actually immune to artificial inoculation altogether. A similar immunity state occurs in birds infected with *Proteosoma*.

ETIOLOGY: GENERAL DESCRIPTION OF THE PARASITES THAT CAUSE MALARIA

The three species of malaria parasites differ from each other in minor points and in their morphology, but the general course of the life-history is the same for all. As regards man, they exhibit



Fig. 1.—Evolution of the tertian parasite, unstained (see text).

two distinct phases—an intracorporeal and an extracorporeal phase. Each species of parasite has its special **intracorporeal life-span**, which may last approximately from forty-eight to seventy-two hours, according to the species.

On examining fresh malarial blood an hour or two before the occurrence of a paroxysm, the parasite is recognized as a pale disc occupying an area within the red blood-corpusele (Fig. 1, *a*),



Fig. 2.—Evolution of the tertian parasite, stained (see text).

while scattered throughout the protoplasm are a number of intensely black, or reddish-black particles, which are now known to be excrementitious material called *hæmozoin*. As the parasite matures the hæmozoin collects into central blocks, round which the proto-

plasm of the parasite arranges itself in segments. When this cycle is completed, the including corpuscle breaks down and liberates the spherules or spores, none of which contains hæmozoin. A proportion of the spores, escaping phagocytosis, attach themselves to other red blood-corpuscles, which they contrive to enter. In the interior of these newly infected corpuscles the young parasites grow at the expense of the hæmoglobin, and exhibit active amœboid movement. By appropriate staining the free spherules are found to consist of a nucleolus, and this again by a lightly tinted covering of protoplasm. As the parasite grows and approaches maturity, the nucleolus enlarges, becomes less defined, and then



Fig. 3.—Flagellated body of malaria parasite (gamete), stained.

disperses ; finally, just before sporulation both nucleus and nucleolus cease to be distinguishable (Fig. 2, *a, j*).

At this stage these elements become fragmented and diffused throughout the protoplasm. Later, the nuclear elements reappear as numerous minute, scattered nucleoli ; and it is around these that the protoplasm of the segmenting parasite arranges itself to form the spherules (Fig. 2, *b, c*). The vesicular character of the nucleus does not usually appear in the spherules until after these have become free in the liquor sanguinis (Fig. 2, *d*).

The hæmozoin particles, characteristic of the malaria parasite, occur as black or very dark-red dust-like specks, coarse grains, or short rods, either isolated or aggregated into larger or smaller, more or less dense clumps. Until the concentration of hæmozoin which

precedes the formation of spherules takes place, the particles are scattered. Apparently, so long as the nucleus remains entire the hæmozoin is peripheral; when segmentation occurs in the nucleus the hæmozoin becomes central.

Extracorporeal or mosquito cycle.—The three species of malaria parasite undergo a similar cycle of development in the body of the mosquito.

First stage.—When fresh malarial blood is examined in a wet preparation shortly after it has been drawn, what is known as the “flagellated body” (Fig. 3) may be observed. The flagellated body¹ is derived from the sexual cells or *gametocytes*;



Fig. 4.—Malaria parasite (gamete): flagellated body and free-swimming microgamete.

composed of colourless protoplasm and hæmozoin granules, it floats freely in the liquor sanguinis. The flagella (or more correctly *microgametes*) number from one to six, or more. They are extremely delicate filaments which move about rapidly, and every now and again break away from the parent body and swim about with vibratile movements (Fig. 4). These bodies are never seen in the fresh blood, but only when it has been removed from the body and has become chilled in the process. The gametocytes of the three forms of malaria parasite differ in shape.

¹ The expressions “flagellated body” and “flagellum,” applied to this phase of the malaria parasite, though graphic enough, are somewhat misleading. The flagella of the malaria parasite are in no sense analogous to the flagella of the flagellata; they really function as spermatozoa. The proper zoological terms for this and the other phases of the malaria parasites are given at p. 700.

In the benign tertian and quartan they are round, while in the subtertian they are crescentic.

Crescents (*see also* p. 27) are never found in the blood at the commencement of a malarial attack, but only after seven to ten days. They are not affected by quinine in the same degree as are the other stages of the parasite. The shape, size, and structure of the crescent body can best be gathered from the illustrations (Figs. 5, 17). It has a very definite crescentic shape, and usually the outline of the remains of the blood corpuscle in which it has developed can be distinguished as a delicate membrane surrounding the parasite. The body shows no amœboid movements, and contains, generally about the centre of the parasite, numerous needle-shaped hæmozoin particles; in some instances they are scattered throughout the parasite, while in others they are concentrated. It has been

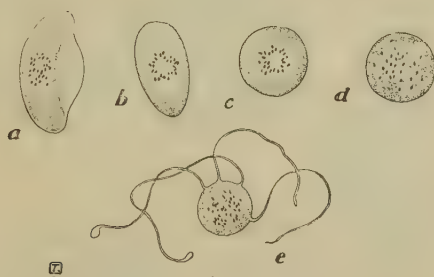


Fig. 5.—Evolution of the flagellated body from the crescent (male gametocyte).

ascertained that these two definite forms of crescent represent a sexual differentiation. In the male type the protoplasm is hyaline, and the hæmozoin loosely arranged; in the female the protoplasm is faintly granular, and the hæmozoin is arranged as a well-defined ring about the centre of the parasite. In the benign tertian and quartan parasites the corresponding sexual cells or gametocytes develop from young ring-forms while circulating in the peripheral blood, thus differing essentially in their mode of development from the crescents of the subtertian (Fig. 6).

When the blood is drawn, the first change that is seen is the conversion of the crescent into the sphere. At the same time the remnant of the red blood-corpuscle which is clinging to the periphery of the parasite melts away. In the male parasite (or male gametocyte) the hæmozoin particles at once become violently agitated; soon the entire parasite, sharing the agitation, is jerked about; and finally, after a variable time, one or more filaments are shot out

from the periphery and indulge in lashing movements. These are the flagella or microgametes (Fig. 5). Inoculation of gametocytes into another individual does not produce malarial infection. This was proved by Mühlens and his colleagues in 1920.

The microgametes themselves are formed of two elements—a chromatic filament and a covering of protoplasm. After they have broken away, the remains of the flagellated body are seen to consist of hæmozoin granules included in a small amount of residual protoplasm, which is usually ingested by some wandering phagocyte.

Conditions favouring and retarding eruption of microgametes.—By exposing the slide to the air with slight aqueous admixture, as by breathing on it before applying the cover-glass, it is generally easy to procure quickly, from crescent-containing blood, specimens of the flagellated body.

In certain bloods the flagellated body is easily procured; in others the

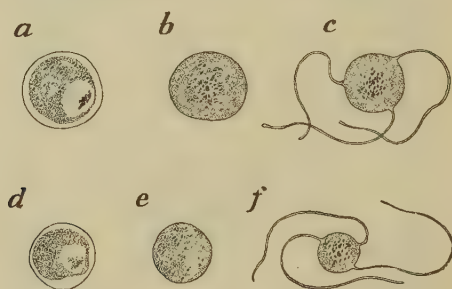


Fig. 6.—*a, b, c*, Evolution of the flagellated body from the respective gametocytes in tertian fever; *d, e, f*, evolution of the flagellated body in quartan fever.

opposite is the case. As regards the crescents, doubtless success depends in a measure on the degree of maturity of the parasite, young or effete crescents failing to evolve. There are other conditions affecting the process, however, which are as yet unknown.

The granular spheres, or female gametocytes, do not project flagella, but on becoming spherical remain quiescent. The object of the microgametes is, after breaking away, to approach and endeavour to enter the granular spheres (female gametes). At one point on the surface of each of the granular spheres a minute papilla can be seen to project, and at this point one of the microgametes contrives to enter, and, after momentarily causing perturbation in the contents of the sphere, comes to rest and vanishes from view. Although the sphere may again be energetically attacked, no second microgamete can effect an entrance. This process, which was first observed by MacCallum, constitutes the act of

impregnation, and subsequently for a short time the granular sphere undergoes no apparent change.

*Second stage. Development of the parasite in the stomach of the mosquito (Fig. 7).—*The impregnated female parasite is now known as a *zygote*. At first spherical in shape, it soon becomes oval and elongated, but finally assumes a vermicular form, the hæmozoin accumulating at the broad or posterior end, while the anterior

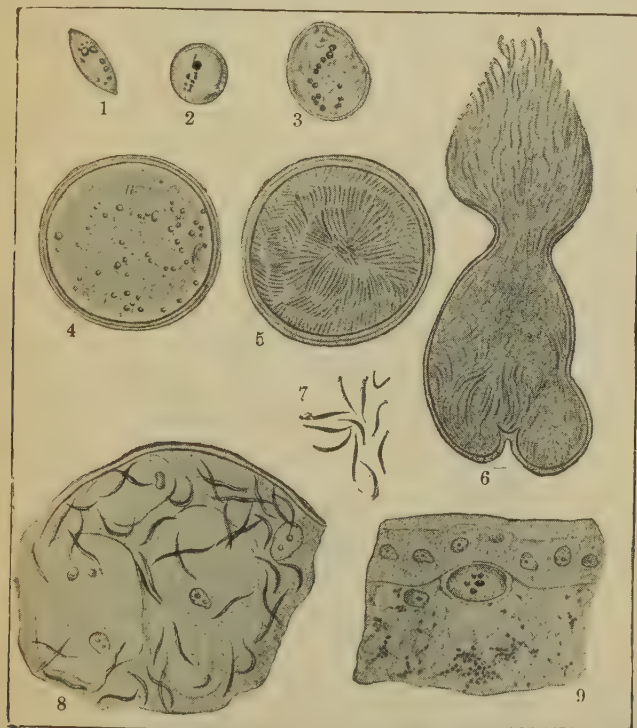


Fig. 7.—Evolution of the crescent parasite in *Anopheles maculipennis*.
(Adapted from Grassi, Bignami, and Bastianelli.)

1 to 6, The parasite as found in the stomach-wall; 7, isolated sporozoites; 8, sporozoites in the salivary gland; 9, section of stomach-wall showing the parasite *in situ*.

becomes pointed and hyaline. It is then capable of independent movement, and is known as the *travelling vermicule*, or technically the *oökinete*. This body moves about rapidly, with the pointed end forwards. Penetrating the wall of the mosquito's stomach, and working its way through the layer of cells and the delicate basement membrane which constitutes the inner coat of this organ,

it comes to rest among the longitudinal and transverse muscular fibres lying between the inner membrane and the delicate outer

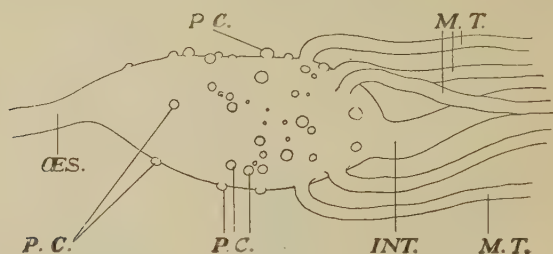


Fig. 8.—Stomach of mosquito after infection with *P. vivax*.

M.T., Malpighian tubes; INT., intestine; ÆS., œsophagus; P.C., oöcysts protruding into the body cavity.

coat. In this situation, some 36 hours after the mosquito has fed, the parasite may be detected as an oval or spherical body, 6 μ

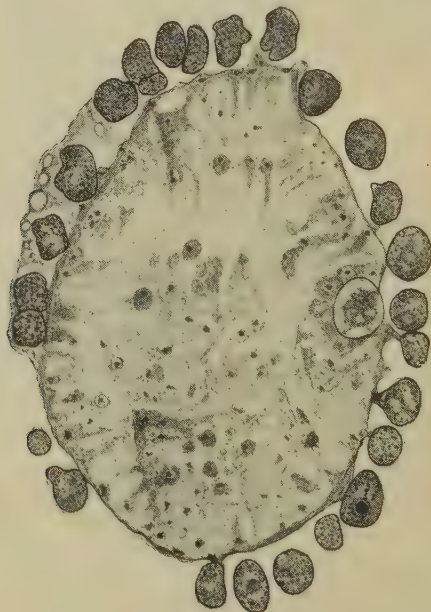


Fig. 9.—Transverse microscopic section of stomach of *Anopheles maculipennis* with numerous oöcysts in presporozoite stage.

(From a preparation by Wenyon.)

in diameter, with a sharp outline, and showing hyaline or slightly granular contents, in which the hæmozoin particles are plainly

visible. During the next few days the parasite increases rapidly in size and acquires a well-defined capsule when, in consequence of its growth, it protrudes on the surface of the mosquito's stomach like a minute wart (Figs. 8, 9), technically known as an oöcyst. The nucleus and protoplasm of the cell now divide into a sort of

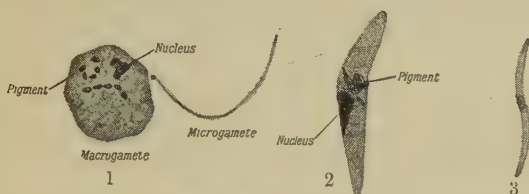


Fig. 10.—Evolution of *Plasmodium falciparum* in *Anopheles maculipennis*. Highly magnified. (After Wenyon.)

1, Fertilization of macrogamete by microgamete of *P. falciparum*; 2, ookinete of *P. falciparum* from stomach of *A. maculipennis* twelve hours after feeding; 3, sporozoite from salivary gland of *A. maculipennis*. Wet preparation.

sponge-work containing protoplasmic masses, around which are formed a vast number of minute, slender, spindle-shaped nucleated bodies, each measuring, when fully formed, $16\ \mu$ in length. At a later stage, from the seventh to the tenth day, or a longer period, according to the atmospheric temperature, the oöcyst becomes filled with these spindles, which lie free inside the capsule, and are now known as *sporozoites* (Figs. 7, 10-3).

Third stage.—The growth of the oöcyst till it reaches its maximum dimensions occupies a period of a week at least, or it may last considerably longer if the temperature is low. It has been shown by Wenyon that development can be arrested by exposure to cold for a short period, but can recommence the moment the temperature is raised. The oöcyst becomes distended, then ruptures, setting free the sporozoites into the body-cavity of the mosquito.

The investigator, on dissecting anopheles, should have no difficulty in recognizing malarial oöcysts, even under a low power of the microscope. They are spherical and very refractile, appearing to jut out beyond the stomach-cells. With a higher power ($\frac{1}{8}$ in. lens) the characteristic pigment can be seen in their interior; in *P. vivax* it is light-yellow, and in *L. malariae* dark-brown in colour. There are various misleading appearances which one must learn to recognize, such as certain large body-

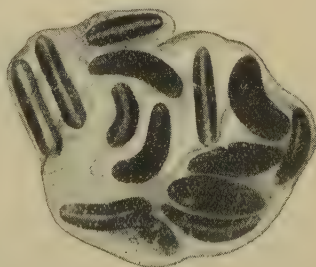


Fig. 11.—Oöcyst of malaria parasite from the stomach of *Anopheles maculipennis* containing Ross's "black spores." (After Wenyon's "Protozoology.")

cells—known as pancreatic cells—gregarine cysts, and even encysted larval trematodes, which occur in the stomach of these insects.

Ross's black spores.—In some infected mosquitoes oöcysts may be encountered which differ in their appearance from normal ones at a similar stage of development. The cyst-wall in their case is filled with dark-brown or black masses, representing undoubtedly the degenerated cell-content, which has become chitinized (Fig. 11). Some observers consider that these spores represent an invasion by a fungus which preys on the oöcysts.

From the body-cavity the sporozoites pass to the three-lobed salivary glands which lie one on each side of the anterior part of the thorax of the insect (Fig. 12). These glands com-

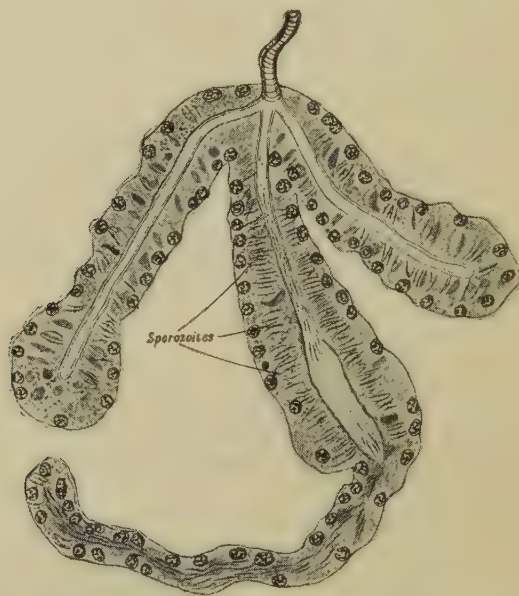


Fig. 12.—Salivary gland of *Anopheles maculipennis* containing sporozoites of *Plasmodium falciparum* compiled from serial sections.

(From a preparation by Wenyon.)

municate by means of a long salivary duct with the base of the mosquito's proboscis (Fig. 13), and it is by this route that the sporozoites escape to the exterior. In the salivary gland itself the sporozoites can be recognized in many of the cells, especially those of the middle lobe, and can also be distinguished in the contents of the ducts. Mayer and Mühlens have shown that under favourable conditions, when oöcysts are numerous in the stomach,

sporozoites are found throughout the body-cavity of the mosquito and scattered in great numbers in the thoracic muscles, even within the palps, scutellum and in other situations.

Transference to the human host.—If a mosquito whose salivary glands contain malarial sporozoites bites a man, the sporozoites are introduced into the blood, penetrate the red corpuscles and multiply, a process which was actually observed by Schaudinn. After eight to ten days their progeny can be seen as malaria parasites corresponding in type to those of the man on whom the infecting mosquito had originally fed.

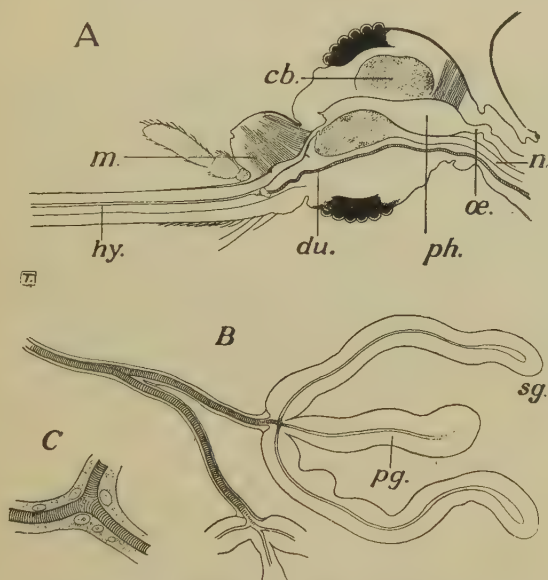


Fig. 13.—Dissection of head of mosquito.

A, Median section of head, showing *du.*, the veneno-salivary duct, with its insertion in *hy.*, the hypopharynx; *cb.*, cerebrum; below this are the cerebellum and the pumping enlargement of *œ.*, the oesophagus; *m.*, muscle; *n.*, nerve-commissure. The other parts have been removed. B, The veneno-salivary duct, showing its bifurcation and the three glands on one of its branches; *pg.*, poison gland; *sg.* marks the upper of the two salivary glands. C, The bifurcation of the duct with its nucleated hypodermis.

Exact observations by Christophers have shown that, in the most favourable circumstances, at the maximum only about 4 per cent. of a suitable anopheline host (*Anopheles culicifacies*) are found naturally infected. Roubaud indicates that *A. maculipennis* is a most propitious host for both *P. vivax* and *P. falciparum*; he found that 39·37 per cent. of the insects became infective with the former, and 50 per cent. with the latter parasite, when fed in captivity upon a suitable case. As regards natural infection of malaria in anophelines, many factors must necessarily be called into play. Amongst these the foremost are the season of the year at which the researches are

carried out, whether malaria is rife at the time and whether the insects have been captured in human habitations or in cattle sheds. Bentley in Bombay showed that 18 per cent. of *A. stephensi* were infected in August, but none in the dry season. Similar variations in infection rate of *A. maculipennis* have been found by Swellengrebel in Holland. King in America found that in the case of *A. quadrimaculatus*, as the result of twelve months' observation, the infection rate was 0.57 per cent., but that in the case of specimens taken in negro huts it was 4.9 per cent. The mere fact that a particular species can be infected in the laboratory proves little as regards its capabilities of transmitting malaria under natural conditions.

Artificial infection of susceptible species of anophelines and technique employed.—For the production of malarial infection in general paralytics by mosquito-bites, James finds it best not to use mosquitoes (*A. maculipennis*) bred from larvæ, but to use specimens collected in the adult stage from stables and other buildings in a country district where malaria does not occur. The insects are collected one by one in test-tubes and transferred to a mosquito cage (see p. 886). When about 300 have been caught, a water-proof cover is drawn over the cage, which is then taken to the laboratory. After removal of the cover, the cage is placed in an incubator at 23° C. for 24 to 48 hours in order that the blood in the stomachs of the mosquitoes may be digested quickly and that they may be ready to feed upon the infecting case. For the case to be suitable for infecting mosquitoes it is essential that the peripheral blood should contain male and female gametocytes in the ripe stage; the male forms should “flagellate” readily in a moist-chamber preparation of freshly-drawn blood (see p. 13).

James finds it best in artificially-inoculated malaria cases, in order to produce a sufficient number of gametocytes of benign tertian for example, to permit the patient to have a number (ten or more) of attacks of malaria before administering a small dose (5 gr.) of quinine. A remission of fourteen to seventeen days will occur before the next attack, when gametocytes in the right stage will be found abundant in the peripheral blood.

When the mosquitoes are to be fed on the infecting case they are taken from the cage in a test-tube and then transferred to glass jars. The tops of these jars should be covered with a piece of paper in which a half-circle valve of the same size as the mouth of the test-tube is cut. In order to liberate the mosquitoes the cotton-wool plug is withdrawn from the mouth of the test-tube at the time the mouth of the tube is pushed through the valve. When the mosquito has flown into the bottle, the tube should be withdrawn and at the same time the valve should be plugged with cotton-wool. After twenty mosquitoes have been transferred to each of

four or five bottles, pieces of mosquito-netting should be laid over the paper which closes their mouths, and by keeping the mosquito-netting in place with the palm of the hand, the paper should be carefully drawn away, thus leaving the netting as a cover to the mouth of the bottle, and it should then be tied on tightly.

The jars containing the mosquitoes are then placed on the leg of the patient in the manner shown in Fig. 14. An attendant should keep the mouths of the jars pressed closely against the skin during the period allowed for feeding, which is usually about twenty minutes. The mosquitoes bite readily through the netting

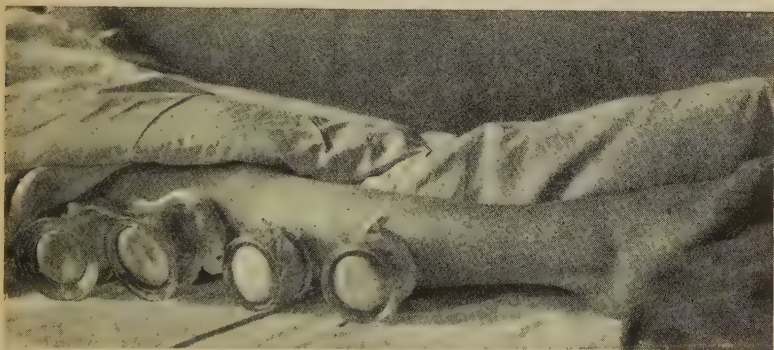


Fig. 14.—Method of feeding mosquitoes used by Col. S. P. James.

(Reproduced from the *Second Malaria Report of the League of Nations Commission*.)

covering the mouths of the bottles. When the mosquitoes have fed, the jars are placed inside the cage and the netting covers removed. The mosquitoes then escape into the cage. The cage is kept in an incubator at 23° C. (73° F.), and by standing a bowl of water in the incubator and hanging wet cloths in it the air is kept as nearly saturated with moisture as is possible. The procedure described is repeated daily, the mosquitoes being fed for at least five days on an infecting case. Afterwards they are fed every day, or every other day, on a patient who is awaiting treatment, in order to ensure that they should obtain the necessary amount of nutriment. Some mosquitoes die every day, and these are dissected to ascertain the progress of the malaria infection. When sporozoites are present in the salivary glands (usually between the tenth and fifteenth day after the first infection feed), incubation is discontinued and the group of insects should be kept

either at room-temperature or in an icebox at 5° C., when further development will be arrested and the mosquitoes will remain torpid, but ready to infect a patient when required. When kept in an icebox during the intervals between successive feedings, some individual mosquitoes will remain alive and infective for a month or longer.

In order to infect a patient, four or five mosquitoes are transferred from the cage to one of the glass jars and allowed to bite the patient in the manner already described. Usually two or three of the mosquitoes bite within a few minutes. When human blood cannot be obtained to nourish the mosquitoes, they can be fed on glucose solution on cotton-wool (p. 886).

By this method James has shown that nearly 100 per cent. of mosquitoes become infective; while the experience of Wenyon in Salonika and that of the Editor in England show that after a single feed on a suitable benign tertian case fully 80 per cent. of *A. maculipennis* develop oöcysts in their stomachs if the air is kept moist and warm. For the technique of dissecting these insects, see p. 887.

Possibility of a latent phase in the human body.—It is a well-established fact that when the fever subsides, the parasite disappears from the general circulation, either spontaneously, or as the result of the administration of quinine. Usually, after an interval of weeks or months the parasite may reappear in the peripheral blood. During this period of latency nothing is known positively of the organ or tissue it selects to hide in.

A possible reservoir of infection?—There are districts in India, Africa and elsewhere that are almost uninhabited on account of the prevalence and virulence of the local malaria. Observers, however, are now of opinion that the malaria parasite, under natural conditions, can be acquired by man only through the bite of the mosquito; that the mosquito can acquire the parasite only by ingesting the blood of a malaria-infected man.

Transmission of the malaria parasite to the fœtus.—Malaria parasites have been demonstrated in the blood of a child before birth (Buckingham), while Heiser has recorded the case of an infant seven days old with crescents of *P. falciparum* in its blood.

Congenital malaria is very exceptional, and probably only occurs when accidental tears of the placenta allow passage of parasites from maternal to fœtal circulation.

Blacklock and Gordon discovered in Sierra Leone that of pregnant women infected with *P. falciparum*, 36 per cent. sustain

intensive infection in the placenta leading to death of the foetus.

THE THREE FORMS OF PARASITES AND THEIR ASSOCIATED FEVERS

There are three clinical types of malarial disease which are associated with three distinct and corresponding species of malaria parasites. These different species have been classified according to (1) the duration of their respective life-cycles inside the human body; (2) their morphological characters; (3) the clinical phenomena to which they give rise; and (4) the results of inoculation experiments.

Benign parasites are of two kinds: the *quartan*, which has a cycle of seventy-two hours and causes a fever that recurs every fourth day, counting from the first day of fever—*quartan fever*; the other, the *benign tertian* parasite, with a cycle of forty-eight hours, causes a fever which recurs every third day, counting in a similar way—*tertian fever*.

TABULAR STATEMENT OF THE CHARACTERS OF THE THREE SPECIES OF MALARIA PARASITE

	Duration of schizogonic cycle	Movement	Hæmatozoin	Trophozoites	Adult schizont	Number of merozoites	Form of gametocytes	Alterations in corpuscles	Relative number of parasites in peripheral and visceral blood	Liability to relapse
1. Benign tertian parasite, <i>Plasmodium vivax</i> .	48 hours.	Active ameboid.	Fine yellowish-brown in colour.	Signet rings of various sizes; growing forms irregular in size, with vacuole.	Larger than a red cell.	14-24, average 18-20.	Round or slightly ovoid, larger than the red cell.	Hypertrophied and pale, stippled with Schüffner's dots.	Parasites numerous in all parts of the body in various stages of their cycle.	Relapses noted up to 31 years from time of original infection.
2. Quartan parasite, <i>Plasmodium malariae</i> .	72 hours.	Slight, in immature forms.	Coarse, dark brown.	Signet rings, as in <i>P. vivax</i> ; growing forms band-like or angular. Vacuole soon disappears.	Slightly smaller than a red cell.	6-12, average 8 or 9.	Round or slightly oval, size of red cell.	Not enlarged, may be slightly contracted; no stippling.	As in <i>P. vivax</i> .	Infection particularly persistent. Relapses may occur for 6 years or more from time of original infection.
3. Subtertian parasite, <i>Plasmodium falciparum</i> (<i>Laverania malariae</i>).	24-48 hours (irregular)	Active ameboid.	Pigment blacker than in other forms; may be aggregated into coarse granules.	Rings small, often containing two nuclei; other forms may be aggregated to edges of red cell.	Distinctly smaller than a red cell.	8-24, sometimes more. Very variable.	Crescentic or sausage-shaped.	Usually unaltered; in later stages paler, sometimes containing coarse dots or irregular mottling (Maurer's dots or clefts).	The greater development of the parasite takes place in the internal organs; hence the relative scarcity of all, save most immature forms, in peripheral blood.	Much less than in other two forms: infection intense in early stages. Relapses may occur after 9 months from time of infection. Maximum period observed, 11 years.

The malignant or *subtertian* parasite is also known as the *æstivo-autumnal*, and has a life-cycle of approximately forty-eight hours.

The characters of the three species are set out in tabular form on p. 23.

The benign tertian parasite, *Plasmodium vivax* (Plates II and V).—In its early stages this parasite assumes a distinct ring-form with large and conspicuous vacuole, and large nucleus, which is situated usually at the thinnest part of the ring; sometimes, though rarely, the nucleus is duplicated so as to form two dots in a signet ring. (These do not represent two distinct nuclei, but merely the original one broken into two fragments.) The diameter of the average ring is about $3\ \mu$, though larger forms may reach to half the size of the containing corpuscle. As it grows, the trophozoite shows great activity, changing its form and location in the corpuscle, insensibly pushing out and retracting pseudopodia (Plate II, B 2). This amoeboid movement persists during the growth and while the hæmozoin is being deposited, though in progressively diminishing degree; and explains the great irregularities seen in the contour of the parasite in stained specimens (Plate V, Fig. 1). The movement is entirely suspended by the time the parasite has reached its full development. The vacuole in which the nucleus is situated, and which is crowded with nutritive chromatin, becomes much smaller as the parasite develops. The parasite grows vigorously for about 40 hours, when it attains its full size. As the parasite grows it obtains its nutriment at the expense of the red cell, and therefore marked changes take place in the protoplasm of the latter. When tertian-infected corpuscles are stained with Romanowsky's stain the protoplasm is speckled with chromophilic particles called *Schüffner's dots*, which are at first very fine, but soon become coarser and more prominent. This is a feature of some diagnostic value, but in the very young phase of the parasite it is not always present. The dots are usually pinkish in colour. Another highly characteristic accompaniment of tertian infection is the considerable enlargement of the infected corpuscles. Sometimes they seem to be nearly twice the diameter of healthy ones; and usually the rim of corpuscular protoplasm surrounding the parasite has a "washed-out" appearance.

Schizogony.—The fully-formed schizont is more or less round in shape, being larger than a normal corpuscle and about $9-10\ \mu$ in diameter. The nucleus is fairly large, often lying near the periphery of the parasite, with the chromatin somewhat diffusely arranged. One or two small vacuoles may still be present. The first stage of schizogony consists of nuclear multiplication, the result of binary fission. The number of merozoites thus formed varies from 14 to 24. This process of multiplication takes 6-8 hours, when the merozoites are liberated from the corpuscle; the cycle therefore lasts for about 48 hours. Complete schizogony coincides with the occurrence of a rigor in the patient.

Gametogony.—After schizogony has continued for a certain period some young trophozoites become sexual forms or gametocytes. It is stated that young gametocytes can be recognized in the earlier stages as small solid forms. Growth is much slower, a gametocyte taking nearly twice as long as a schizont to become adult, and, moreover, no vacuole is developed in the cytoplasm. The growing parasite is less active, and hence it does not exhibit the manifold changes of form seen in the growing schizont. The quantity

PLATE II

MALARIA PARASITES. $\times 2,000$.

A.—SUBTERTIAN PARASITE (*Plasmodium falciparum*).

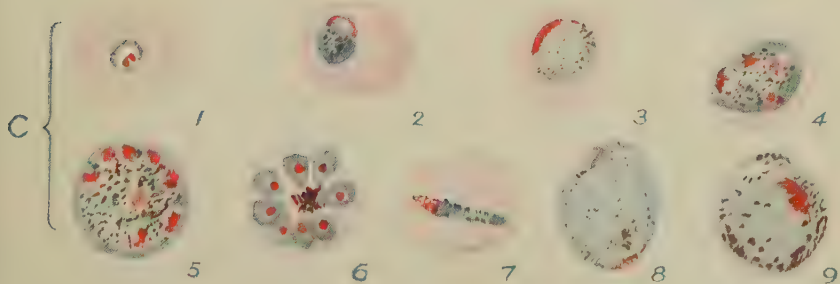
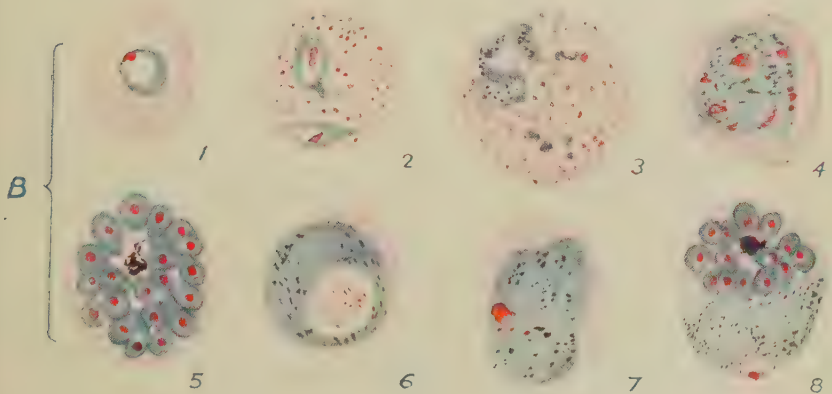
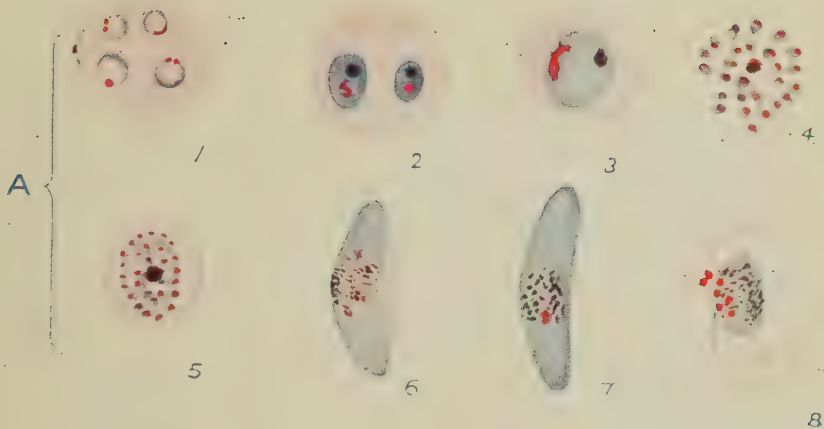
- Fig. 1.—Subtertian rings, heavy infection. Note the marginal form, and in some the double chromatin dots.
- Fig. 2.—Parasites thirty hours old, approximately, from a brain smear. At this stage they become arrested in the capillaries. Note early and characteristic concentration of pigment.
- Fig. 3.—Parasite forty hours old, from an artificial culture; forms seen usually in the capillaries of internal organs.
- Fig. 4.—Complete schizogony, with separation of merozoites, from spleen smear.
- Fig. 5.—Complete schizogony, from brain smear of a fatal case.
- Fig. 6.—Male gametocyte (crescent), with remains of red cell, from peripheral blood.
- Fig. 7.—Female gametocyte (crescent), staining a darker hue, with concentration of chromatin and pigment.
- Fig. 8.—Exflagellation of male gametocyte.

B.—BENIGN TERTIAN PARASITE (*Plasmodium vivax*).

- Fig. 1.—Young ring form in peripheral blood.
- Fig. 2.—Amœboid forms. Note the Schüffner's dots and a slight enlargement of corpuscle.
- Fig. 3.—Amœboid form, a quarter grown. Note formation of pigment in cytoplasm, Schüffner's dots, and increased size of corpuscle.
- Fig. 4.—Schizont, showing early division of chromatin.
- Fig. 5.—Complete schizogony in peripheral blood, with formation of twenty merozoites.
- Fig. 6.—Male gametocyte. Note loose arrangement of chromatin, pale cytoplasm, and smaller size than female.
- Fig. 7.—Female gametocyte. Note compactness of chromatin, and darker-staining cytoplasm.
- Fig. 8.—Double infection of single corpuscle with gametocyte and schizont.

C.—QUARTAN PARASITE (*Plasmodium malariae*).

- Fig. 1.—Young ring form.
- Fig. 2.—Partially-grown form; compact parasite with coarse pigment.
- Fig. 3.—A more fully-grown stage than Fig. 2.
- Fig. 4.—Early division of chromatin in young schizont.
- Fig. 5.—More fully-grown schizont, with chromatin divided into eight masses. Note coarse and scattered pigment.
- Fig. 6.—Complete schizogony, showing typical rosette with centrally-placed pigment and formation of eight merozoites.
- Fig. 7.—Characteristic "band form" of young quartan parasite.
- Fig. 8.—Male gametocyte.
- Fig. 9.—Female gametocyte, with coarser pigment and darker-staining cytoplasm.



John Gordon Thomson, pinx.

MALARIA PARASITES (Leishman's Stain).

of pigment produced is also much greater, the granules of the macrogametocyte being more numerous and larger than in the adult schizont. The macrogametocyte is much larger than the mature schizont, being 12-14 μ in diameter, while the microgametocytes are much smaller. There are other distinguishing features in the microgametocyte: the nucleus is large and diffuse, spreading across the body in the shape of a spindle; the cytoplasm is hyaline, and stains a lighter colour; while the nucleus of the macrogametocyte is small, compact, and stains more deeply, and the cytoplasm is granular, non-vacuolated, and stains an intense blue. As a rule, macrogametocytes are more numerous in the blood than microgametocytes.

Plasmodium vivax is capable of maintaining itself (after a single infection) in the human body for a period of about three years, after which it dies out.

Quartan parasite, *Plasmodium malariae* (Plate III, Fig. 1).—This parasite has a cycle in the peripheral blood of 72 hours. The young trophozoites usually have the signet-ring appearance, and are indistinguishable from the same stage of the tertian. At this stage it is capable of but feeble



Fig. 15.—Quartan parasite, asexual cycle : stained.

amoeboid movement, hence the irregular forms so frequently met with in the tertian are not found in the quartan. Later, as soon as it becomes pigmented, all the amoeboid movement ceases (Fig. 15 and Plate II, c), and it grows across the corpuscle, producing a characteristic ribbon- or band-shaped appearance. Even the nucleus itself becomes elongated at this stage.

The changes produced in the corpuscle differ from those seen in the preceding infection. The red cell does not enlarge, but tends to contract and becomes slightly smaller than the average. Schüffner's dots do not occur. The hæmoglobin is darker brown and coarser in appearance, and the oscillation of the pigment granules is less marked than in benign tertian.

Schizogony.—The adult schizont is distinctly smaller than the corresponding phase of the benign tertian, rarely exceeding 6.5 μ in diameter. The parasite does not occupy the whole of the red cell. Nuclear division begins after the schizont has been growing for 48 hours, and takes place comparatively slowly. The number of merozoites is small, varying from 6 to 12; their arrangement is symmetrical, giving rise to a daisy-head appearance. The individual merozoites are larger than in the benign tertian and average 1.75 μ in diameter. The segmenting schizont of the quartan parasite is more frequently seen in the peripheral blood than is the corresponding phase of the other malarial parasite. For this reason, and because of the easy visibility of the parasite in all its stages, owing to the large amount of

hæmzoin it carries, the quartan is the best form of malaria for the beginner to study.

Gametogony.—The growing gametocytes do not assume the band form of the growing schizont. The young macrogametocyte is heavily pigmented, and contains a smaller amount of chromatin than a schizont of the same size, but the microgametocyte has more chromatin and a lighter-staining cytoplasm. Adult quartan gametocytes usually occur but scantily in the protoplasm, the microgametocytes being particularly rare. The mature macrogametocyte completely fills the red blood-corpuscle, scarcely a rim of cell-protoplasm being visible, so that it looks at this stage as if it were a free and independent body floating about in the liquor sanguinis. The microgametocyte contains a very large amount of chromatin, and is slightly smaller than the female form. The quartan parasite is capable of maintaining itself in the human body for a longer period than the benign tertian and may persist for six or seven years.

The subtertian or malignant parasite, *Plasmodium falciparum* Blanchard (Plate II, A). *Synonym: Laverania malaricæ*.—A notable feature in the differentiation of this parasite is its much smaller size, the rings averaging 1.25 to 1.5 μ in diameter. The earlier phases, owing to their minuteness, and partly owing to the thinness of the cytoplasm, are difficult to see. (Fig. 16, a.) The rings are usually sharp and regular in outline, the chromatic



Fig. 16.—Evolution of the subtertian parasite: asexual cycle.

nucleus being often divided into two—a very characteristic feature in stained preparations, which may distinguish it from the younger forms of the benign tertian parasite. Multiple invasion of individual corpuscles is often encountered, much more frequently than in the benign infections, doubtless due to the prodigious number of parasites which may be present. Another characteristic of the young subtertian parasite is the position in which many of them attack the host-cell, applying themselves to the margin or edge of the corpuscle. These are known as “accolé” or “appliqué” forms. Frequently they appear as short streaks of cytoplasm with red nuclear dots, giving them a bacilliform appearance, the vacuole not being visible. (Plate IV and Plate VI, Fig. 1.)

At this stage, unless the observer has had a great deal of experience, the parasite is apt to be missed, for it may be the only form appearing in the peripheral circulation. As the development advances, the invaded corpuscles are filtered out by the capillaries and small arteries of the deeper viscera and of the bone-marrow; they are especially numerous in such organs as the spleen and the liver. In heavy infections a few more mature forms than the ring can be found, and very occasionally a fully-segmenting schizont. Rarely

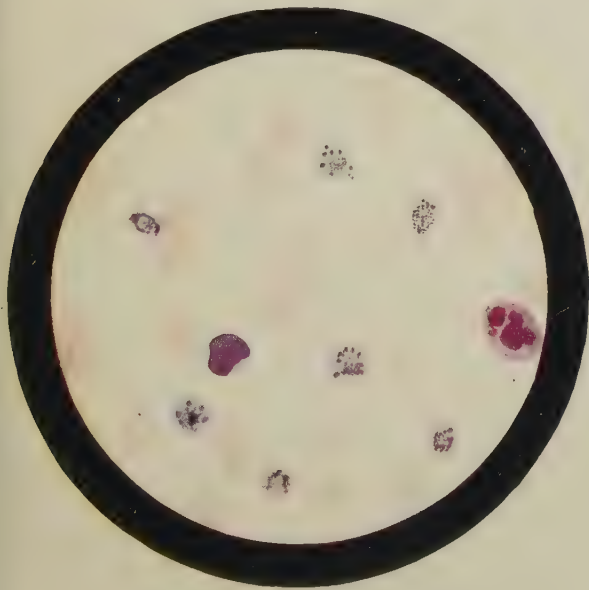


Fig. 1.—Blood-film of quarten parasite, showing sporulating bodies and developmental forms.

(J. K. Lund, del.)

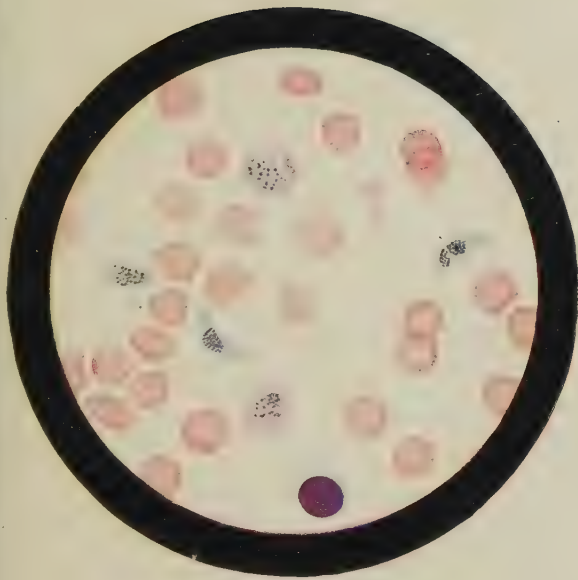


Fig. 2.—Blood-film of a double infection with the benign and subtertian parasite, showing crescents and developing benign forms.

THE BLOOD PICTURE IN MALARIA, QUARTAN AND MIXED INFECTIONS. (Gauducheau's stain.)

cases are met with in which all stages of schizogony may be observed in the peripheral circulation. As a rule, it is necessary to aspirate splenic blood, or to search the bone-marrow or viscera—liver, spleen, or kidney—immediately after death, in order to find examples of the more advanced stages of the parasite. (Fig. 16, c, d, e, f.) It is difficult to fix the duration of the life-span of these parasites, but it is probably one of 36 hours.

In the case of *P. falciparum* the size of the host-cell remains practically unaltered. Schüffner's dots do not occur, but occasionally other brick-red or pink dots, which are larger and more irregular in shape than Schüffner's, become apparent; they are usually known as Maurer's clefts. When seen in the fresh state the infected corpuscles have a slightly darker look, which is said to resemble old brass, and hence they have been referred to as "brassy

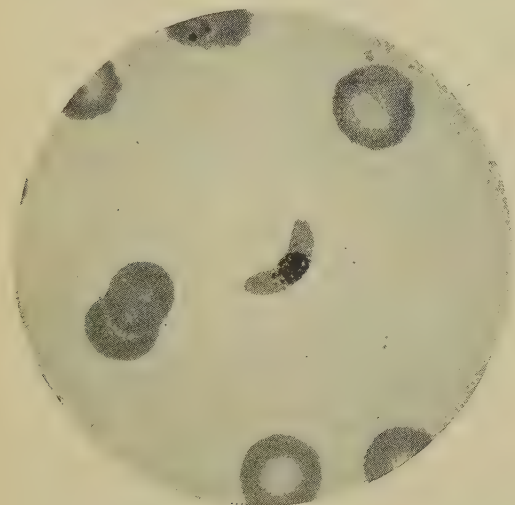


Fig. 17.—Female crescent in subtertian malaria. $\times 1,000$.

(Microphoto: Dr. A. Norman.)

bodies." The hæmozoin in the growing schizonts occurs in well-developed blocks, and usually appears as one dark and conspicuous mass.

Schizogony generally occurs in the capillaries of the internal organs. (Plate VII, Fig. 2.) The adult schizont commonly measures $4.5-5\ \mu$ in diameter, and a large part of the host-cell is unoccupied. Nuclear division takes place rapidly, and the number of merozoites produced, even in the same infection, varies very greatly. They usually number from 8 to 24. (Fig. 16, g.) The merozoites themselves are smaller than those of the benign tertian parasite, and average from 0.7 to $1\ \mu$ in size. Schizogony does not proceed at the same uniform rate as in the case of the other types. Apparently it may take anything from 36 to 48 hours to accomplish.

Gametogony.—The gametocytes of this parasite assume the well-known crescent shape which has already been referred to (p. 13), but it should be pointed out that the term crescent is not absolutely correct, for the ends are not, as a rule, pointed; their shape, in fact, is much more like that of a

sausage, with rounded ends. They are fairly large bodies, ranging from 9 to 14 μ in length by 2-3 μ in breadth. It is believed by some that a definite capsule is secreted around the crescent bodies (J. D. Thomson), and that they are produced mostly in the capillaries of the spleen and bone-marrow. The crescents are not seen at the onset of the infection, but once they begin to appear in the peripheral blood they generally tend to increase in numbers during the next few days. Being much less amenable to the action of quinine than are other stages or types of the malaria parasite, they may persist in the blood for as long as six weeks after the subsidence of the fever. According to Sinton the life-span of the crescent is 30-60 days. However, it has been noted that quinine, if given sufficiently early in the course of a subtertian attack, may prevent the crescents from appearing in the peripheral blood. Crescents are readily killed off by the drug plasmoquine and its compound with quinine (*see* p. 76).

The two sexes can be distinguished. The *male* is broader than the female, while its nucleus is diffuse and may occupy the greater part of the body, but the contained hæmozoin is scattered throughout the cytoplasm. The *female*, the more slender of the two, has a small centrally-placed nucleus, while the hæmozoin tends to be concentrated round about it. (Fig. 17.) When the crescent is mature the substance of the contained red blood-corpuscle is entirely used up, so that only the corpuscular envelope persists, and in this the parasite lies. Sometimes the outline of the cell may be observed staining faintly on the margins of the crescent; very rarely, twin or double crescents are seen in one corpuscle (Fig. 18).

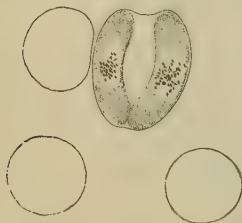


Fig. 18.—Subtertian parasite; twin crescents.

It is a singular fact that in many of the worst types of tropical malaria—as that of tropical Africa—crescents are few in number, and in some instances cannot be found by ordinary examination. Plehn states that during a period of two years in Africa he only once saw the flagellated body. On the other hand, when we meet with these African infections in England crescents are frequently encountered, and often in great abundance; at all events, this is a general experience.

In primary infections under suitable conditions, crescents appear in the peripheral blood about the third week.

The young gametocytes can be distinguished from schizonts of the same age by their elongated shape, and by the fact that the pigment is scattered, and not aggregated into one mass. The nucleus is small and situated towards one end of the parasite, and usually extends as a cross line along one edge of the body, in very much the same way as in the quartan. Subsequently the nucleus passes towards the centre of the body.

The subtertian parasite has a much shorter life in the human body than the two species previously considered; at the most a single infection survives from one month to one year.

Abnormal appearances of the malaria parasites.—Quite frequently, mixed infections of two (Plate III, Fig. 2), and very rarely all three, forms of parasite can be found in the same individual; the usual combination, however, is the benign tertian with the subtertian infection. The immature forms of both parasites may

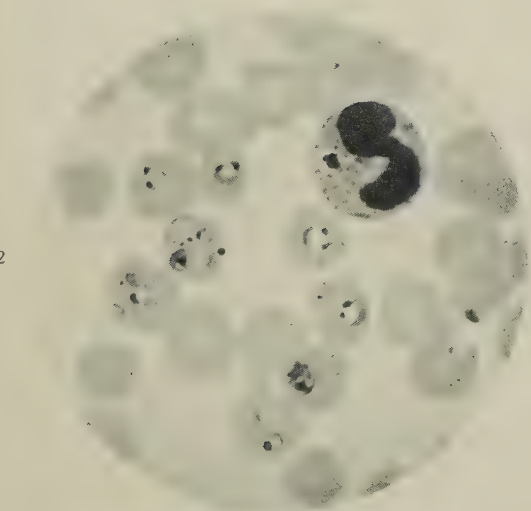
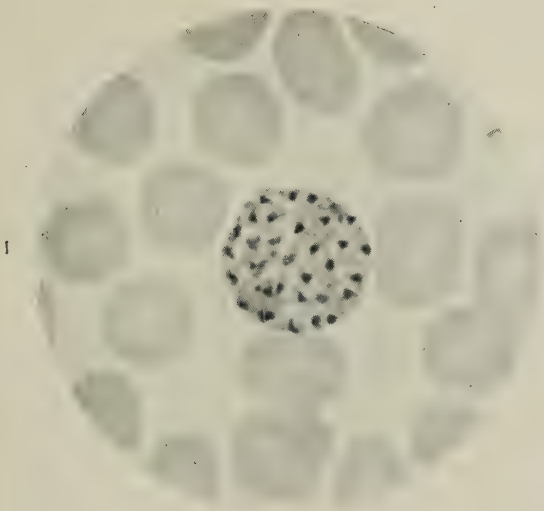


Fig. 1.—Corpuscles containing two sporulating bodies of the benign tertian parasite. $\times 1,800$.

(Microphoto: Dr. A. Norman.)

Fig. 2.—Subtertian rings, punctate basophilia, Maurer's clefts, and a pigmented leucocyte. $\times 1,000$.

(Microphoto: Dr. A. Norman.)

(From specimens by Dr. J. D. Thomson.)

MALARIA PARASITES (Stained).

be found in the same microscopic field, but most usually one sees the various developmental stages of the benign tertian parasite combined with the crescents of the subtertian; very rarely the two different species of parasites have been observed in the same cell. Combined infections of benign and quartan may also be encountered. Certain puzzling appearances have been noted by observers since the time of Schaudinn, which were thought by him to represent a further stage than those already described as denoting a process of parthenogenesis, but these were shown by J. D. Thomson to represent two schizonts (both possibly segmenting) infecting the same red blood-corpuscle. Combined infection of schizont plus male or female gametocyte, or even two gametocytes, within the same red cell, has also been observed (Fig. 19). Double, triple, and even quadruple infections of the same red blood-corpuscles by subtertian rings are quite commonly observed in heavy infections (Plate VI).

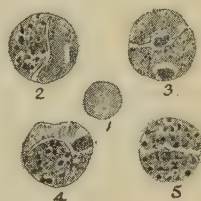


Fig. 19. — Abnormal malaria parasites.

(After Dr. J. D. Thomson.)

- 1 Normal red corpuscle; 2, gametocyte and schizont; 3, gametocyte and gametocyte; 4, gametocyte and schizont; 5, schizont and schizont, both undergoing schizogony.

Cultivation of the malaria parasite.—The cultivation *in vitro* of the malaria parasite was first effected by Bass, in 1911, and subsequently confirmed by the brothers Thomson. The method is described on p. 865.

Asexual multiplication of the parasites has been observed in all three types of malaria, and in the case of the subtertian parasite as many as four successive generations have been cultivated in this manner. Recently Sinton has grown crescents of the subtertian parasite in artificial culture of blood after 10 days' incubation (*see* p. 866). Several interesting points have been observed in the morphology of the cultivated parasites. The number of merozoites formed during schizogony is considerably greater than in the parasite under natural conditions, while the growing parasites of the subtertian form show a remarkable tendency to clump together, a phenomenon not observed in the benign tertian type.

CLINICAL PHENOMENA OF MALARIA FEVER

Formerly the malaria fevers were divided into intermittent or remittent forms (*see* p. 34), but it has since been found that intermittency or remittency is more or less an accident, for any of the three parasites already described may cause what was formerly known as remittent fever. Two generations of tertian parasites maturing on two successive days will produce a quotidian fever; but two generations of quartan parasites maturing on successive days will give rise to fever on two successive days followed by one day of freedom from fever—what is known as *Quartana duplex*;

whereas three generations maturing on three successive days will produce a quotidian fever—*Quartana triplex*.

Each attack of malaria fever consists of a stage of coldness or rigor (ague), a stage of heat, and a stage of sweating; these are followed by a period of apyrexia known as the interval. The duration and intensity of these constituent stages vary very considerably.

Premonitory stage.—Before rigor sets in, and sometimes for several days before the actual disease declares itself, there may or there may not be a premonitory stage marked by lassitude, a desire to stretch the limbs and to yawn, aching of the bones, headache, anorexia, perhaps vomiting, perhaps a feeling as of cold water trickling down the back. If the thermometer be used, it will be found that body-temperature has begun to rise, it may be some two or three hours before the other and more striking symptoms which ensue set in; or it may be that the threatened attack will subside spontaneously without culminating in the more pronounced phenomena of a fully-developed ague.

Cold stage.—When rigor sets in, the feeling of cold spreads all over the body, becoming so intense that the teeth chatter and the patient shivers and shakes from head to foot. He seeks to cover himself with all the wraps he can lay hands on. Vomiting may become distressing. The features are pinched, the fingers are shrivelled, the skin is blue and cold-looking, and may exhibit the condition known as “goose-skin” (*cutis anserina*). But the feeling of cold is entirely subjective; if the temperature be taken, it is found to be already several degrees above normal and to be rapidly mounting. In young children it is not at all unusual to have a convulsive seizure at this stage—a fact that has to be borne in mind, as it is very apt to suggest ideas of epilepsy.

Hot stage.—After a time the shivering gradually abates, giving place to, or alternating with, waves of warmth and, before long, to persisting feelings of intense heat and febrile distress. The wraps, which before were so eagerly hugged, are now tossed off; the face becomes flushed; the pulse is rapid, full, and bounding; headache may be intense; vomiting frequent; respiration hurried; the skin dry and burning, the thermometer mounting to 104°, 105°, 106° F., or even higher.

Sweating stage.—After one or more hours of acute distress the patient breaks out into a profuse perspiration, the sweat literally running off him and saturating his clothes and bedding. With the appearance of diaphoresis the fever rapidly declines; headache, vomiting, thirst, and febrile distress giving place to a feeling of

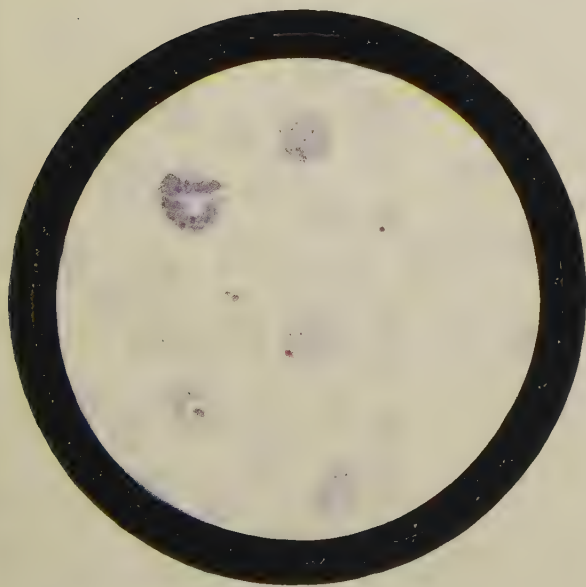


Fig. 1.—Blood-film showing parasite in various stages.

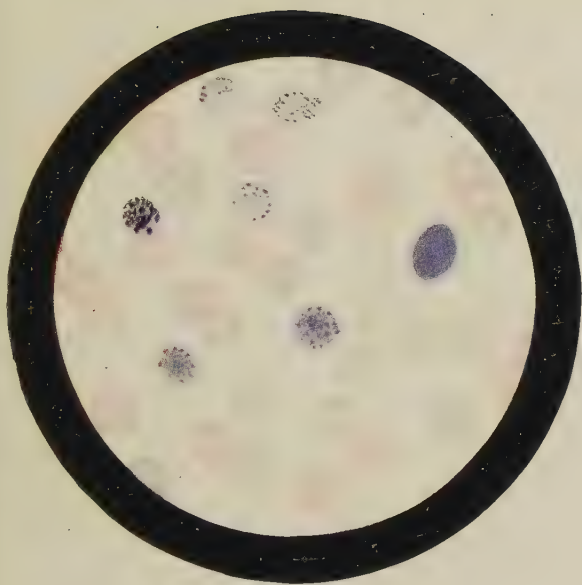


Fig. 2.—Blood-film showing sporulating bodies and gametocytes.

(J. K. Lund, del.)

THE BLOOD PICTURE IN BENIGN TERTIAN MALARIA. (*Leishman's stain.*)

PLATE V

relief and tranquillity. By the time the sweating has ceased the patient may feel quite well; a little languid, perhaps, but able to go about his usual occupation. The bodily temperature is now often subnormal, and may remain so until the approach of the next fit, one, two, or three days later.

Duration of the fit.—The duration of an ague fit and of its constituent stages is very variable. On an average it may be put at six to ten hours, the cold stage occupying about an hour, the hot stage from three to four hours, the sweating stage from two to four hours.

The urine in ague.—During the cold stage the urine is often limpid and abundant, and is passed frequently; but during the hot, sweating stages it is scanty, loaded, sometimes albuminous. The amount of urea is increased, particularly during the cold stage, and so are the chlorides and sulphates. The phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. The augmentation in the excretion of urea commences several hours before the subjective symptoms of the attack begin, attains its maximum towards the end of rigor, and decreases during the hot and sweating stages, although still continuing above the normal standard. The excretion of carbonic acid follows a corresponding course. The urine usually contains urobilin.

The spleen during the fit.—The spleen becomes enlarged to a greater or less extent during rigor. At first the swelling disappears in the interval, but it tends to become more or less of a chronic feature if the attacks recur frequently, more especially if they are associated with pronounced cachexia. Spontaneous rupture of the spleen may occur, though rarely, after injury to the abdomen, necessitating splenectomy. The operation, however, does not extirpate the malarial infection, as has sometimes been stated. Hennessy has noted that the symptoms of rupture of the spleen may simulate those of rupture of the bladder owing to the presence of pain in the hypogastrium and the irritation of the bladder.

Period of the day at which ague commences.—A large proportion of agues “come off” between midnight and noon, or in the early afternoon. This is a fact to remember in diagnosis; especially when we have to face the possibility of recurrent pyrexial attacks being dependent on such conditions as liver abscess, tuberculosis, and septic states—conditions, be it remarked, in which febrile recurrence takes place almost invariably during the afternoon or evening.

Atypical agues.—Some cases of subtertian malaria, especially of African origin—liable to assume suddenly a pernicious character—are of this nature. On the other hand, notwithstanding a comparatively slight rise of temperature, headache, prostration, or vomiting may be extremely distressing. There is an infinite variety in this respect.

Terms employed.—Acute malarial attacks which recur daily are called *quotidian ague*; if they occur once in 48 hours, they are called *tertian ague* (Chart 1); if once in 72 hours, *quartan ague* (Chart 2). As a rule, the attacks tend to occur about the same time every day. When the fit is prolonged and periodicity is marked by only a slight fall of temperature, a slight sweating, a slight feeling of chilliness, the fever is said to *remit*—to be *remittent*. Sometimes there is no remission; such a fever is said to be *continued*. When a fever oscillates above and below the normal line from day to day, it is said to be *intermittent*.

All sorts of blendings of subtertian with tertian, and occasionally of either or both with quartan, may occur; these are cases of *mixed infection* (see p. 36).

Relation of the phenomena of the fever to the developmental stages of the parasite.—During the rigor the segmenting parasites are breaking up and are liberating the merozoites, which escape into the peripheral blood. At the end of the rigor and during the hot and sweating stages, the young parasites of the new generation—small and intracorpuseular bodies or schizonts—and pigmented leucocytes containing the hæmozoin liberated by the breaking-up of the fully-formed schizont, can be demonstrated.

During the apyrexial interval, the intracorpuseular parasites are growing in size, becoming pigmented, and preparing for maturation. From the fact that parasites are present in the blood during apyrexia, often in great numbers, it is evident that it is not the mere presence of the parasite in the blood-corpusele which causes the fever; the pyrogenic agent is in the nature of an anaphylactic or “hæmoclastic” shock. Abrami and Senevet have applied this term to a condition resulting from the inoculation of foreign proteins into the blood-stream; the phenomena consisting chiefly of lowered arterial tension, leucopenia, a diminution in the number of red cells and changes in the coagulability of the blood. Most probably the showers of liberated merozoites or the products of the destroyed red blood-corpuseles act as a foreign protein injected into the blood-stream.

The explanation formerly given to correlate the various stages of the malaria parasite with the clinical aspects of the case have not received much support from recent experience. Owing to the work of Wagner-Jauregg of Vienna, the treatment of general paralysis of the insane and other grave nervous disorders is being carried out by the injection, subcu-

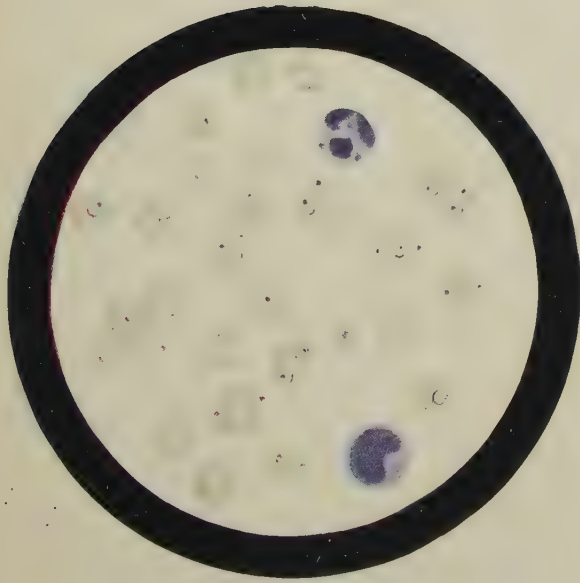


Fig. 1.—Blood-film from fatal case of subtertian malaria, showing heavy "ring" infection. (*Giemsa's stain.*)

(*J. K. Lund, del.*)

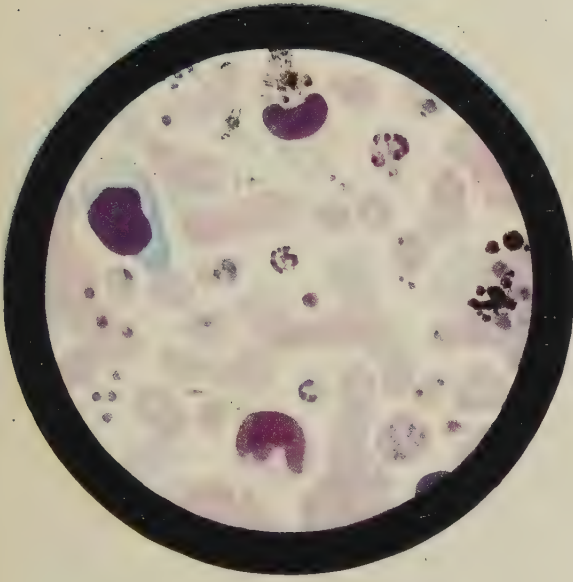


Fig 2.—Spleen smear from same case, showing large numbers of developing parasites, sporulating bodies, and malarial pigment. (*Leishman's stain.*)

THE BLOOD PICTURE IN SUBTERTIAN MALARIA.

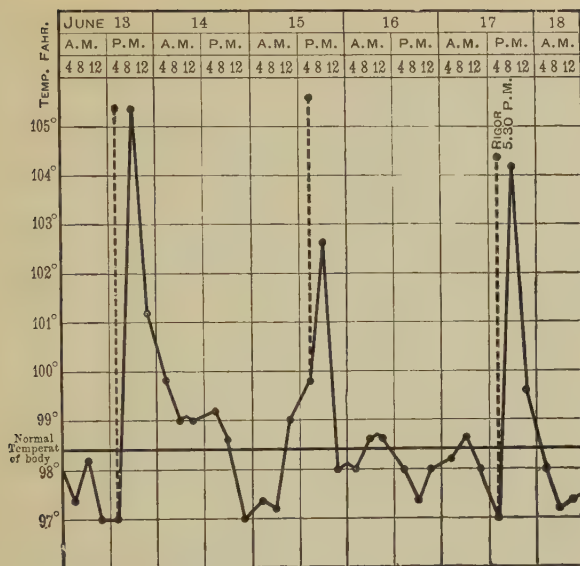
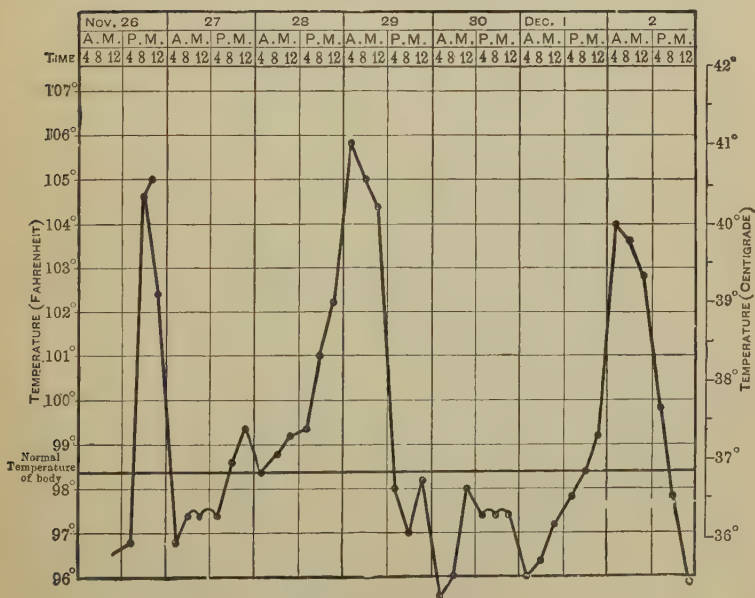


Chart 1.—Benign tertian ague.



D

Chart 2.—Quartan ague.

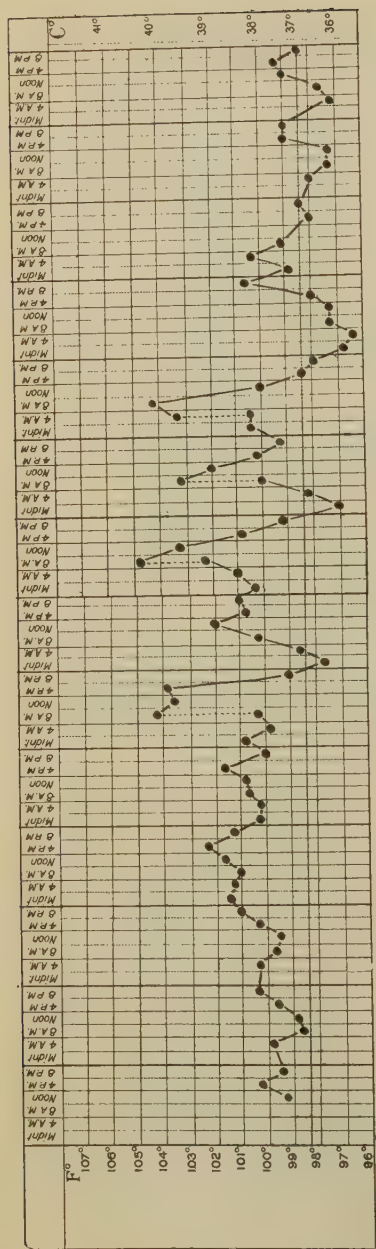


Chart 3.—Inoculated benign tertian malaria, showing initial remittent pyrexia. (Dr. G. C. Low.)

taneously or intramuscularly of 1 to 2 c.c. of blood containing benign tertian parasites,¹ with the consequent production of attacks of malaria in the person thus injected. Considerable amelioration of the clinical symptoms has been noted, which possibly may be attributed to the "protein shock" thus produced, while a great deal of information regarding the behaviour of the benign tertian parasite within the body and its clinical effects has been accumulated. Eight to twelve malarial attacks are regarded as the optimum. After numerous "passages" (as many as sixty) without the intervention of the mosquito host, the parasites can be found in large numbers in the blood-stream without having altered in any way in morphology or in virulence. Artificial malaria may also be produced by the bite of an infected mosquito or by the actual subcutaneous injection of the extract of the insect's salivary glands containing sporozoites. Contrary to the opinion formerly held, it has been shown that inoculation of sporozoites from the salivary glands of one infected anopheles will produce in some persons *quotidian* rigors due to parasites sporulating within a day of each other. In many cases, also, after an incubation period of 7-10 days the onset of the malaria attacks is characterized not by typical intermittent fever, as seen in Charts 1, 2, but by a *remittent* fever which may persist for a week or more before becoming frankly intermittent (Chart 3). This feature appears to have been noted in the historic

¹ It is most important that only *P. vivax* strains should be used; deaths have occurred from inoculation with *P. falciparum*. Favourable results have been recorded in Vienna from the employment of the *Treponema duttoni* of relapsing fever in place of malaria.

inoculation experiments originally carried out by Manson and Grassi, to which reference has been made (p. 2). The results of this form of treatment have, according to Yorke and Macfie, been favourable: 27·4 per cent. of general paralytics were regarded as temporarily cured, while in a further 20·2 per cent. great physical and distinct mental improvement were observed. It has been proved that stabilization takes place so that re-adaptation to family life and social responsibilities is possible. In other forms of cerebro-spinal syphilis, it would seem as if malaria therapy acts as a mordant for the specific medication employed.

In inoculated infections disinfection by quinine is extraordinarily easy. To effect a complete cure, the amount of quinine administered has varied from 45–150 gr. Relapses after subcutaneous inoculation of malaria are extremely rare, while in naturally-acquired malaria they are almost the rule. It seems therefore that malarial infection produced by the injection of sporozoites is much more long-lived and much less amenable to quinine. Valuable information has also by these means been obtained of the failure of quinine to act in a prophylactic manner. The administration of quinine in 10-gr.-solution daily for five days previous to, the day of, and eight days after the bite of infective mosquitoes fails to prevent the development of malaria; similar results have been obtained in cases where 30 gr. of the drug in solution were given on the day of feeding infective mosquitoes and on each of the two following days. These experiments show that quinine has no action upon the sporozoites injected by the mosquito; on the other hand the development of malaria can be prevented by 10 gr. of quinine daily taken for ten days after the infecting bites.

COURSE OF BENIGN TERTIAN AND QUARTAN FEVERS

Benign tertian fever usually lasts ten hours or less and corresponds to the description already given, although all sorts of variations of a typical attack may occur; in some cases the rise of the fever is rapid and high, and the temperature may reach 105° or 106° F. within an hour or so. On the other hand, cases are met with in which none of the clinical phenomena of malaria fever are present, and the temperature does not rise above 99–100° F. The fever in quartan infection is generally smart while it lasts, and well defined as regards the various stages, but it does not tend so markedly as in other malaria infections to the rapid development of cachexia. It has often been noted that although individual attacks of this infection are amenable to quinine, the disease itself appears to be of a more persistent nature than tertian or subtertian malaria. Attacks, therefore, are prone to recur during several years. The parasites too, are more resistant to quinine in one sense, in so far as they persist in the blood-stream for a week or more whilst the patient is taking quinine. There is some evidence that quartan malaria is more prone to be associated with subacute nephritis than are the other forms of malaria.

As a general rule, the duration of one benign tertian infection

is nine months to a year after leaving the endemic area, before the parasites die out from the peripheral blood, but exceptions to this rule often occur; clinical relapses, with the presence of the parasite in the blood, have been recorded as long as three and even four years after the date of the original infection. Quartan is the most resistant and persistent infection of the three.

CHARACTERS OF SUBTERTIAN OR MALIGNANT FEVERS

From a clinical point of view as regards diagnosis and treatment, this is the most important form of malaria met with. As a rule, the fever produced is very irregular in its course. *The rigor stage is relatively less marked*; the pyrexial stage is more prolonged, and is often characterized by a tendency to adynamic conditions, together with vomiting, intestinal catarrh, pains in the limbs, anorexia, severe headache, and depression. After apparent recovery from the fever there is a great proneness to relapse at more or less definite intervals of from eight to fourteen days, but an immunity soon appears to develop. Experience gained during the Great War has tended to show that benign tertian infections are, as a rule, far more persistent than are the subtertian. Subtertian fevers are accompanied by rapid destruction of corpuscles, and are usually followed by marked cachexia. At any time in their course, but more especially during primary infections, symptoms of the gravest character may declare themselves.

As a general rule, the associated symptoms are in many respects very different from those caused by the tertian parasite. In the first place, although rigor is not so marked, the hot stage lasts longer—often exceeding twenty-four hours; in fact, the tendency for the successive paroxysms to overlap, to become subintra, is very marked. Moreover, when the intermissions are distinct the crisis is generally unlike that of ordinary tertian. There is frequently what is called a *double crisis*; that is to say, when the fever has attained its apparent fastigium there is a drop of one or more degrees of temperature—the “false crisis”—to be followed by a fresh rise, which is then succeeded by the “true crisis.” This peculiar phenomenon has been attributed to the presence of two swarms of parasites, one of which matures somewhat later than the other; it is only proved to occur regularly in one other tropical fever, namely, kala-azar. (Chart 4.)

A double infection with the subtertian parasite may produce a quotidian fever (Chart 5), a typhoid-like depression generally being a marked feature.

This form of fever is justly regarded as being dangerous to life, yet in certain instances the parasite may exist even in considerable numbers in the blood-stream for months on end without seriously

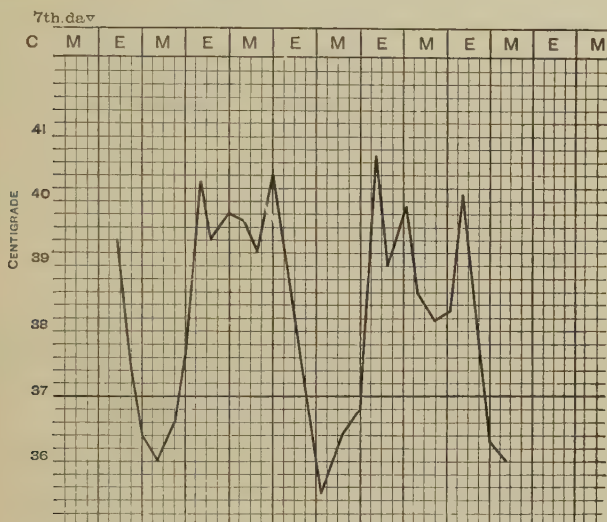


Chart 4.—Subtertian fever (*P. falciparum*).

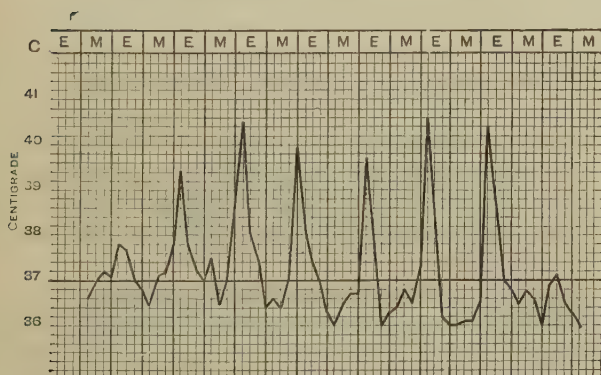


Chart 5.—Quotidian fever (two generations of *P. falciparum*).

interfering with health; it may produce no ascertainable rise of temperature, or the patient may eventually seek medical aid suffering from cedema of the legs, dyspepsia, or some other bizarre

or trifling complaint apparently quite unconnected with malaria. Cases of this nature are frequently seen in men returning from the West Coast of Africa, in whom the first symptoms of ill-health may appear after several months' residence in England. As the infection is capable of lying dormant for a long period, one should examine microscopically the blood of every patient coming from a malarious country, whatever the nature of his complaint. Though subtertian malaria may produce the most virulent infections and may be in many instances a danger to life itself, yet individual infections are much more amenable to quinine than are the benign tertian. The life of the parasite in the human body is much shorter, and it is extremely rare for relapses of subtertian malaria to be noted nine months to one year after quitting the endemic area of the disease.

The clinical guises which subtertian malaria may assume are most protean in character. It may markedly simulate many other tropical fevers, and even surgical conditions. The following are the main clinical types of this fever recognized :

Bilious remittent.—One type of malarial fever, bilious remittent, has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhœa, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish-yellow or saffron tint of skin and scleræ—a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified hæmoglobin (hæmaphein) free in the blood or deposited in the skin and sclerotics. These bilious remittents are very common in the more highly malarious districts of Africa, America, the West Indies, India, and, in fact, in all malarious tropical countries. They are not usually directly dangerous in themselves, but they are apt to result in profound anæmia, and are often but the prelude to chronic malarial saturation, bad health and invaliding.

A modification of the bilious remittent—the “typhoid remittent”—is very much more grave, as affecting life, than the simple bilious remittent. In the typhoid remittent, typhoid symptoms—such as low delirium, prostration, dry tongue, swelling of spleen and liver, subsultus tendinum, marked melanæmia—are superadded to the usual symptoms. Though recovery is the rule, a considerable proportion of such attacks prove fatal.

Some writers class by themselves a set of cases they call “adynamic remittent”—cases which are characterized by fatuousness, restlessness, nervous depression, intense muscular and cardiac debility, profound and rapid blood deterioration, icterus, liability to syncope, occasionally a transient hæmoglobinuria (as was observed in some of the Salonica cases), liability to hæmorrhages, and a marked tendency to local gangrene.

Tuberculosis, syphilis, renal disease, or alcoholism will often be found as factors in determining the adynamic remittent and typhoid remittent types of fever.

Pernicious attacks.—Many writers have drawn attention to what are called pernicious attacks or pernicious symptoms—the French neatly designate them *accès pernicieux*—a series of phenomena of which the possibility, not only in the course of remittents but in the course of what is seemingly only an ordinary paroxysm of intermittent fever, should never be lost sight of by the practitioner in tropical climates. These *accès pernicieux* may supervene in apparently mild cases and carry off the patient with horrifying suddenness—as suddenly as an attack of malignant cholera. The wary practitioner is always on the look-out for them, and is always prepared with measures to meet them properly when they threaten.

Pernicious attacks are roughly classified into cerebral and algid. The cerebral are divisible into hyperpyrexial, comatose, convulsive, paretic, and so forth; the algid into syncopal, choleriform, hæmorrhagic, etc.

CEREBRAL FORMS. *Hyperpyrexia.*—There can be little doubt that many of the cases of sudden death from hyperpyrexia and coma, usually credited to what has been called “ardent fever” or “heat-apoplexy,” are really malarial in nature. If careful inquiry be made into the antecedents of many of these cases, a history of mild intermittent fever will often be elicited; or it will be found that the patient had been living in some highly malarious locality.

In the course of what seemed to be an ordinary malarial attack the body-temperature, instead of stopping at 104° or 105° F., may continue to rise and, passing 107° , rapidly mount to 110° or even to 112° . The patient, after a brief state of maniacal or, perhaps, muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours, or perhaps within an hour, of the onset of the pernicious symptoms.

Coma.—Sometimes the patient, without hyperpyrexia, the thermometer perhaps not rising above 104° , or even so high, may lapse into coma. The coma may pass away with crisis of sweating; on the other hand, an asthenic condition may set in and death from collapse supervene. In these cases there is a marked increase of pressure in the cerebro-spinal fluid.

Malarial amblyopia.—In rare instances a comatose pernicious attack eventuates in blindness. The amblyopia is usually transient, lasting for an hour or two only. On the other hand, it may

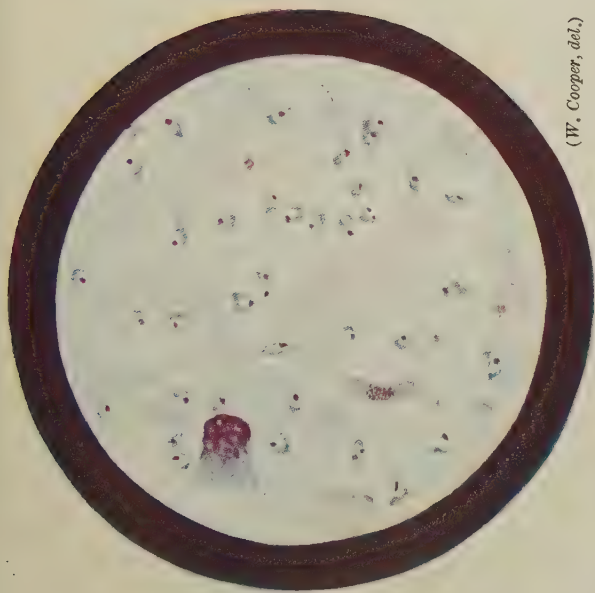
be persistent ; in which case optic neuritis, peripapillary œdema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hæmorrhages, may be found in the fundus. If the hæmorrhages are minute they are discoverable by the microscope only. These fundus changes differ from those in quinine amblyopia. In the latter, depending on retinal anæmia from toxic spasm of the arterioles, the amblyopia is more persistent ; the discs are white and the vessels shrunken ; there are no inflammatory symptoms ; and central vision is the first to recover.

OTHER CEREBRAL FORMS.—Besides these hyperpyretic and comatose conditions, other forms of cerebral attack may occur in the course of malarial fevers. Thus, there may be *sudden delirium* ending in coma and, perhaps, death ; *convulsive seizures* of an epileptic or of a tetanic character, with or without delirium or coma—forms especially common in children, and too often misdiagnosed, with fatal consequences ; conditions simulating *cerebro-spinal meningitis* ; *delusional insanity* ; *dementia* ; *acute alcoholism* ; various forms of *apoplectic-like* conditions and of *paralysis*, complicated, it may be, with *aphasia*. Seizures of this description, if not fatal, may eventuate in *permanent psychical disturbances* with a tendency to *suicide*. Temporary debility, or even complete *loss of memory*, may succeed severe malarial infection.

Embolism of cerebral capillaries.—These cerebral attacks are now explained, and, it appears, correctly explained, by the supposition, founded on actual post-mortem observation, that they depend on embolism by malaria parasites of the capillaries of the various nerve-centres involved : in hyperpyrexia, the thermic centres ; in aphasia, Broca's convolution. Monoplegia or hemiplegia, and so on, may result from implication of special brain areas. By microscopical examination of properly prepared sections of the brain in fatal cases, such a plugging of the vessels can, as a rule, be readily observed. (Plate VII, Fig. 2.) In association with this condition focal degenerations of the brain substance also have been noted (p. 59).

ALGID FORMS.—The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface of the body, and a tendency to fatal syncope. These symptoms usually coexist with elevated axillary and rectal temperature.

Gastric form.—This may be associated with, and in a measure be dependent on, acute catarrhal dyspeptic trouble. It is accom-



(W. Cooper, del.)

Fig. 1.—Thick blood-film preparation of subtertian rings and crescent stained by Leishman to show appearances after dehaemoglobinization. $\times 1,000$.

(From a preparation by Dr. H. Seidelin.)

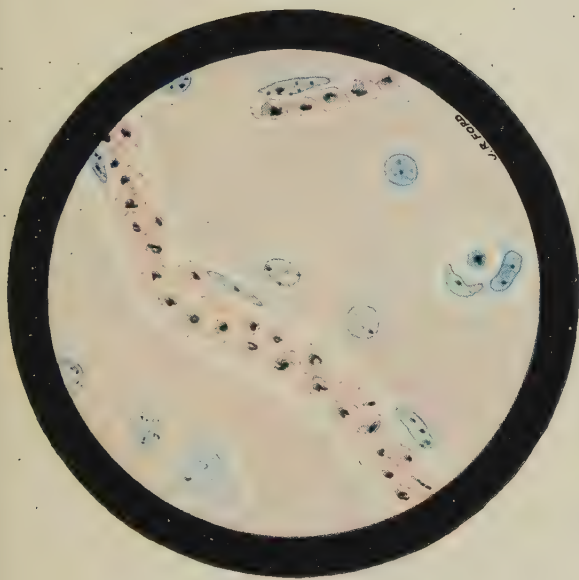


Fig. 2.—Brain section showing sporulating forms of *Plasmodium falciparum* blocking capillaries of cortex. (Gauducheau's stain.)

SUBTERTIAN MALARIA.

PLATE VII

panied by severe epigastric distress, tender retracted abdomen, and incessant vomiting. The vomited matter may contain blood.

Choleraic form.—Malarial attacks are sometimes accompanied by choleraic symptoms. The stools suddenly become loose, profuse, and numerous. They are not generally so profuse or colourless as the rice-water discharge which pours from the patient in true cholera; they retain a certain amount of biliary colouring, and may be mucoid, or even bloody. As in cholera, the serous drain may lead to cramps in the limbs, loss of voice, pinched features, "washerwoman's fingers," almost entire suppression of urine, and perhaps to fatal collapse. Such attacks are very deceptive and may be mistaken for true cholera. The high axillary temperature, if present; a history, maybe, of recent ague fits; the subsequent rapid cessation of choleraic symptoms on the appearance of the hot and sweating stages; the colour of the stools, and other collateral circumstances, usually suffice for diagnosis, particularly if they are supplemented by a microscopical examination of the blood. Although not usual, recurrence of the choleraic symptoms may take place at the next fever period. This dangerous type of malarial fever was noted in Salonica and Palestine during the Great War, and is said to be prevalent in the Punjab. Without the microscope its true nature may be hard to recognize.

Dysenteric forms.—Another form of pernicious attack is characterized by the sudden appearance of dysenteric symptoms, by severe and recurring hæmatemesis, or by hæmorrhage from the bowel or elsewhere. The possibility of a suddenly developed hæmorrhage from the bowel of this nature being of malarial origin must therefore be kept in view; particularly if, in what at first sight appears to be ordinary dysentery, the axillary temperature is found to be abnormally high.

Hæmorrhagic forms.—As in purpura, so in these pernicious attacks, hæmorrhages may occur in almost any organ. When this takes place in the brain or spinal cord it may produce a monoplegia, a diplegia, or even a complete hemiplegia. The effect of these paralyzes may be transient or permanent. Cases of this nature occurred in Salonica and other war areas.

Purpuric hæmorrhages into the skin may be generally distributed over the body. They are of rare occurrence, and are commonly associated with better-known phenomena of malaria fever.

Syncopal form.—In the preceding types of pernicious algid malarial attack the dangerous symptoms mostly show themselves in the rigor stage of the fever. There is yet another form in which the danger appears to depend on an exaggeration of the symptom

usually hailed as bringing relief and, for the time, freedom from danger. Thus the sweating of the stage of defervescence may be excessive and cause collapse which, if the patient rise up suddenly or make an undue effort, may lead to fatal syncope. Weak and cachectic patients, therefore, should be warned of this possibility. Death from suddenly developed cardiac failure is common in the pernicious forms of subtertian malaria, and is due to the severe toxic fatty degeneration of the myocardium (Dudgeon and Clarke).

Acute hæmolytic anæmia.—There is a rapidly developing and progressive anæmia in the fourth or fifth week of a primary subtertian attack, comparable only to what is seen in the most advanced stages of pernicious anæmia. These cases are characterized by great pallor of mucous membranes and conjunctivæ, cardiac distress and dyspnœa, hæmic murmurs, and retinal hæmorrhages; the blood picture by a blood-count of under 1,000,000, extreme leucopenia, a reduction of hæmoglobin to 10 per cent. or under, and the appearance of microcytes and megaloblasts in the blood. The pathology of these conditions indicates the hæmolytic nature of the malaria toxin and its action upon the bone-marrow, which shows megaloblastic response (Fairley and Dew). In consequence of the bone-marrow changes and the inhibition of leucocyte production, sufferers from subtertian malaria are more susceptible to secondary infections of all kinds.

Rarer forms of subtertian malaria.—Pulmonary forms have been described with congestion of the pulmonary vessels and bronchitic symptoms. Rare cases with rapidly developing anasarca and ascites were observed in Macedonia and in Palestine during the Great War; and, lastly, œdematous forms with nephritic signs, such as the presence of blood-cells in the urine, have been noted. Gangrene of the toes, and disturbances in the vaso-motor mechanism, as in Raynaud's disease, have been met with in subtertian malaria.

A practical experience of these suddenly developed pernicious fevers of the tropics teaches that we should never make light of any malarial attack, particularly if it be of a mild irregular character and imperfectly controlled by quinine, and if small parasites, or the crescent form, be present; the practitioner should be on the alert for any danger signal—mental aberration, restlessness, tremor, peculiarity in behaviour, alteration in knee reflexes, and other indications of grave implication of the nervous system. It further teaches that the subjects of such fevers should be particularly careful to guard against chills, fatigue, insufficient or unwholesome food, etc.

Complications.—Subtertian malaria may complicate, or be complicated by, almost any other disease; a common and very fatal terminal event is pneumonia of either the lobar or bronchopneumonic variety, noticeable in the influenza epidemic of 1918. When associated with enteric, this greatly complicates the clinical picture. The same may be said of the main forms of dysentery. Pulmonary tuberculosis is very prone to supervene in cachectic cases. It should be noted, too, that a malarial relapse may take place after any surgical operation, or after parturition, or shock or strain of any description, in a subject previously infected; and the surgeon in the tropics would do well to bear this fact constantly in mind.

A phenomenon occasionally observed in pernicious attacks, especially in those of an algid type, is the flooding of the peripheral blood with vast numbers of parasites, it may be at all stages of development—gametes as well as schizonts. The prognosis in such cases is usually bad. On the other hand rare instances are seen when this occurs in an attack of average severity.

CHAPTER II

MALARIA (*Continued*) AND BLACKWATER FEVER

Synonyms of Blackwater Fever.—Malarial Hæmoglobinuria ; Hæmoglobinuric Fever.

The disease consists in an acute hæmolysis of the red blood-corpuses which liberates the hæmoglobin into the blood-stream, and in turn produces hæmoglobinuria. There are certain points of analogy between this complication of malaria and the disease known as *paroxysmal hæmoglobinuria*.

Geographical distribution of blackwater fever.—There has been much discussion as to the supposed peculiarities of the distribution of this fever. It is apparently very common in some malarious districts but not in others ; we now know this to be due to the prevalence or otherwise of the subtertian parasite in these areas. Although blackwater fever has a wide general distribution, it is limited in its endemicity to low, swampy grounds ; and although, as reported by several authors, it sometimes occurs at high altitudes, this does not prove that infection took place there. The disease has attained its greatest notoriety, and is undoubtedly most prevalent, in Europeans on the West Coast of Africa, from Senegal to the Quanza, but principally on the Congo and in the deltas of the Niger and Gambia rivers. On the East Coast it is also widely spread, especially along the Zambesi, the lower Shiré, and the shores of Lake Nyasa. It is far from uncommon on the Upper Niger, in British East Africa (including the Tanganyika Territory), in Uganda, in North and South Rhodesia, in Abyssinia, and in the valley of the Upper Nile and Algeria. It is also common in some parts of Madagascar.

In America it is found, but not so extensively as formerly, over the southern states of the Union, chiefly Florida, Georgia, Alabama, Mississippi, Arkansas, and Texas ; but recently it has also been prevalent in North Carolina and Virginia. It is found, too, in Central America, on the Upper Amazon, in the plains of Venezuela, and in the West Indies, but it has disappeared from the Canal Zone since the introduction of anti-malaria measures.

In Europe it is restricted to Bulgaria, Macedonia, Albania,

Greece, Sicily, and Sardinia. A few cases may have been recorded in Central Italy.

In Asia it is reported from Palestine, especially the Jordan valley, from Tonquin, the Malay Peninsular, Formosa, from India, particularly Bihar, Assam, Darjeeling, the Terai, Dooars, Meerut, and Amritsar, from Burma and Northern Siam, and from the province of Yunnan, China. It occurs in many of the malarious islands—Java, Solomon Islands, etc.—of the Eastern Archipelago, and also in New Guinea.

Blackwater fever occurs not uncommonly in England in individuals of both sexes who have been infected with subtertian malaria in West Africa and other highly malarious countries. In these people it is apt to break out after exposure to cold, overdosage with alcohol or quinine, within a period as long as five months after their arrival in a temperate climate. Such cases are, as a rule, very acute and the mortality-rate is 50 per cent. or even higher.

Epidemiology.—At times blackwater fever appears to assume an epidemic form. It may not be seen for years in a district, and then numbers of cases may occur within a short time. Very often, as is the case in yellow fever, the magnitude of an "epidemic" may depend on the number of susceptible persons—new arrivals, it may be other than Europeans—within the endemic region; as, for instance, Bengali clerks in the Punjab, Egyptians in the Sudan, Chinese imported into British Guiana, negroes in Panama, and Central African natives when taken to the high altitudes of the great African mountains. Thus it broke out among the labourers employed in making the canal through the Isthmus of Corinth, and attacked the Chinese labourers on the Congo Railway. It is recorded that more than 60 per cent. of the medical casualties in the German East African force under von Lettow were due to blackwater fever.

The occurrence of several cases in the same family may not be pure coincidence, but probably is explained by exposure to a common factor. This has given rise to the term "blackwater-fever houses" in certain districts, especially in Rhodesia, but when investigated they are proved to be bungalows with exceptionally bad surroundings, and highly malarious.

Etiology.—The etiology of blackwater fever has been the subject of considerable controversy, much of which is now a matter of history. At present it is generally recognized to be the result of repeated attacks of, or continuous infection with, subtertian malaria. It is, however, necessary to mention the ideas that have

been put forward, under the headings of specific theory, quinine theory, and malaria theory.

Specific theory.—Quite a number of observers from time to time have described spirochaetes (*Leptospira*) in the blood during the acute stage of the disease, but these appearances have been shown to be due to faulty observation, and are due to the fragmentation of the red blood-corpuscles and the liberation of spirochaete-like filaments from their margins (see Fig. 397, p. 884). On the other hand, a condition resembling blackwater fever has been described by Schüffner and Snijders in Sumatra. The patient died twenty hours from the onset, and leptospiræ resembling *L. icterohæmorrhagiæ* were found in all organs, but especially in the liver, spleen and kidney; in the latter situation they occurred within the urinary tubules. Benign tertian parasites were present in the blood as well, while inoculation of blood into guinea-pigs produced a transitory pyrexia, but not the deep icterus of Weil's disease.

Quinine theory.—The quinine theory of blackwater fever arose in Greece in 1858, and has been upheld more or less vigorously ever since, especially by Koch. Those who favour this theory believe that quinine, even in small doses, may produce the manifestation of blackwater fever in patients in whom the malaria infection is latent. But quinine, even in poisonous doses, never produces blackwater fever in healthy people or in persons uninfected with the subtertian parasite, and a special hypothetical idiosyncrasy has therefore to be assumed. Possibly the issue has been confused by the fact that in susceptible, but otherwise normal, individuals the administration of quinine produces a transient hæmoglobinuria, but this condition is certainly not the same as blackwater fever. In quinine intolerance this drug can produce hæmoglobinuria, as in the instances cited by Manson, Gordon Thomson and Macmillan; whenever it is given, hæmoglobinuria develops within an hour. It has sometimes become necessary to issue a special certificate to such individuals warning medical officers against the exhibition of quinine to them. The fact remains that blackwater fever was known long before the introduction of cinchona bark into Europe; indeed, it was known to Hippocrates.

Malaria theory.—The prevalence of blackwater fever in malarious regions and its occurrence chiefly in persons who have previously suffered from this disease, the finding of malaria parasites and hæmozoin in the peripheral blood and that of the organs, and the rise and increase in the number of mononuclear leucocytes are the facts that have led to the belief that blackwater fever is due to an unusually severe form of malaria. It is also known that, although blackwater fever is co-endemic with malaria in several regions, it is not so in all parts of the world. It has its own peculiar distribution, being absent or very rare in many fever-haunted places. It is exceedingly common among the few Europeans who live on the West Coast of Africa, and it is also met with on the East Coast, though to a lesser extent; but it is practically unknown among the many thousands of Englishmen who live in the fever haunts of India and elsewhere, and it is of comparatively frequent occurrence in malaria-infected individuals shortly after their arrival in a temperate climate from the tropics. The classical researches of Deeks and James in Panama, those of Arkwright, Lepper, Dudgeon, and more recently of Gordon Thomson in Rhodesia and the Editor in London, have shown that the subtertian parasite is the one invariably associated with black-

water. They have shown that, if examined at the right stage, subtertian malaria parasites in the ring-form may be demonstrated in the blood before hæmolysis has occurred, but that during the process of hæmolysis the corpuscles containing the parasites are broken up and destroyed, so that they can no longer be demonstrated. In fact, in some cases the occurrence of blackwater fever brings about a complete cure of the malaria infection from which the patient had previously suffered. Gordon Thomson has investigated over 100 cases in Rhodesia, and the evidence that subtertian malaria and blackwater fever are one and the same disease is almost overwhelming. In that country blackwater fever occurs solely in the districts infested by the subtertian parasite, and in individuals who are infected with it. Furthermore, the prevention of subtertian malaria abolishes blackwater fever. To Deeks and James in Panama must be given the credit of definitely associating the subtertian malaria parasite with blackwater fever and of successfully demonstrating that measures devised for suppressing malaria are singularly efficient in extirpating blackwater fever.

Predisposing causes of blackwater fever.—Individuals of all ages and both sexes are liable, but from consideration of the facts already put forward it is obvious that it occurs more frequently in European men of mature years who live in the countries where the disease is endemic. At one time race was considered an important factor. In Africa, Europeans, Indians, and Chinese are attacked, while the natives enjoy a relative immunity : this is probably not racial but an active immunity acquired by infection with subtertian malaria during childhood. Negroes who live in places which are free from this disease develop blackwater fever as readily as Europeans, if they are exposed to the same conditions.

Plehn mentions serious outbreaks of blackwater fever among negroes on the Cameroon mountains, those who come to the coast from the interior being especially attacked.

Other predisposing causes are debility from previous illness, bad food, hardships of all kinds, dysentery, etc. It has been stated again and again that Europeans are rarely attacked within the first year of residence in a blackwater-fever country, though cases have been reported after so short a residence as three or four months, and exceptional attacks may develop in those who have not previously shown definite symptoms of malaria.

Of a similar nature is the dramatic occurrence of blackwater fever in apparently healthy persons who have arrived in England at the expiration of their duty, or on leave. Instances of this kind have frequently come under the Editor's personal observation, and they may, or may not, be preceded by a typical attack of malaria ; but as often as not the patient gives no previous his-

tory of fever while in residence on the West Coast of Africa, or elsewhere. The explanation of these cases appears to be that the subtertian malaria infection is lying latent until aroused into activity by the exposure to cold, alcohol, or some other factor. Circumstances such as these invariably explain the occurrence of blackwater fever outside the endemic area of the disease.

It has been noted that this disease observes a rough seasonal incidence; it is especially frequent in late summer and in autumn in the southern states of the American Union. On the West Coast of Africa it appears to be most prevalent at the close of the rainy season, or in August and September; in Central Africa and Nyasaland, especially in the highlands, a maximal incidence is seen during the wettest months, May to August, when the lowest temperatures are registered. In Southern Rhodesia, where the hot rainy season and the dry cold season are sharply defined, the malarial incidence increases following the rains in April: that of blackwater fever immediately rises also, and is maintained from March to July. During the Great War, in Salonica and in Palestine cases of blackwater fever occurred among the troops solely during the cold winter months. This coincides, as has already been said, with the incidence of the disease in England.

Mechanism of hæmolysis.—The mechanism of the production of hæmoglobinuria in blackwater fever can only be given in rough outline, as there are various points that are not yet settled. A liberation of hæmoglobin into the plasma—hæmoglobinæmia—most certainly takes place, and can be demonstrated if the blood serum is examined the moment the attack occurs; probably by the time hæmoglobin appears in the urine a large proportion of the red blood-corpuscles has already been completely destroyed. The exciting cause is undoubtedly an acute dissolution of subtertian parasites, but researches in the pre-blackwater stage have failed to demonstrate any constant changes in the constitution or morphology of the red blood-corpuscles, though Gordon Thomson is of the opinion that certain altered corpuscles exhibiting Maurer's clefts, and deformities known as "brassy bodies," are more commonly observed than in uncomplicated cases of subtertian malaria; all that is certainly known is that in severe cases 60–80 per cent. of the red blood-corpuscles in the body are destroyed within twenty-four hours. Apparently the process is largely a physical one, and the dissolution of the hæmoglobin into the blood-stream does not take place until a certain degree of change has occurred in the resistance of the red blood-corpuscles to osmotic

tension. The hæmoglobin is thus excreted by the kidney, and causes the typical cylindrical plugs in the renal tubules, which represent coagulation of highly albuminous hæmoglobin-containing exudate. The hæmolysis is rapidly accompanied by the appearance of bilirubin in the blood-stream. This accounts for the characteristic icterus of the disease. At the onset of blackwater fever there is usually a sudden and noticeable contraction of the spleen, and it is possible that the hæmolytic substances are set free into the circulation from this organ, but the question still remains to be answered: what occasions this reaction—what pulls the trigger? It has been shown that the administration of quinine may cause this contraction and may also cause destruction of a certain number of erythrocytes, but it certainly will not explain *every* case.

It has been shown by Neave Kingsbury, employing the Van den Bergh reaction, that in 90 per cent. of cases of uncomplicated subtertian malaria the serum bilirubin is above the normal figure, which is taken as 0.5 units, and consequently urobilin derived from the serum bilirubin is found in pathological amounts in the urine of these cases. In blackwater fever and in severe subtertian malaria this excess of bile leads to bilious vomiting. Under normal conditions the reticulo-endothelial system of the body deals with the products of hæmolysis by splitting the hæmatin (the iron-containing part of hæmoglobin) into an iron-free pigment, bilirubin, and an iron-containing pigment, hæmosiderin. The bilirubin is excreted by the liver, resulting in an increased flow of bile. The enlargement of the spleen in malaria and in the blackwater fever state may be due to the hypertrophy of the reticulo-endothelial system, and at the onset of blackwater fever the spleen is usually very large and tender. Normally, in a severe case of subtertian malaria there is hæmoglobinæmia, or the liberation of free hæmoglobin into the blood-serum, but this is immediately dealt with by the reticulo-endothelial system, while in blackwater fever the liberation of hæmoglobin is so extensive and so rapid that the renal threshold for free hæmoglobin is broken down and the pigment appears in the urine. It is important to realize that even when hæmoglobinuria occurs, most of the hæmoglobin is broken up by the usual mechanism and only a relatively small proportion—17 to 36 per cent.—is excreted in the urine.

Dudgeon has shown that hæmolytic substances can be extracted from the tissues, and actually from the urine, in blackwater fever, and that similar substances can also be extracted from cases of subtertian malaria. According to recent experimental work by Blacklock the initial cause of the hæmolysis may be the liberation of sarcolactic acid into the blood-stream, such as occurs after fatigue and muscular exercise.

Plehn's theories.—On the other hand, Plehn believes that, owing to repeated destruction of parasites during febrile attacks, the body becomes supersensitive to the protein of the malaria parasite, and that when this

supersensitiveness has attained to a sufficiently high degree the further solution of quite a small number of parasites may precipitate the crisis. These considerations, he believes, allow of no other interpretation than that the hæmolysis takes place in the kidneys, causing a great disturbance in their function, with the production of the well-known pathological appearance in these organs. As indicative of this functional disturbance, it is pointed out that the kidneys are no longer able to excrete bilirubin, which is present in the blood of blackwater-fever cases and also that the specific gravity of the urine is extraordinarily low, from 1001 to 1005.

Yorke and others consider that these changes in the kidneys are due to the irritative effect of the passage through them of a large amount of hæmoglobin, and that no disturbance of the urinary function takes place previous to the production of hæmoglobinæmia.

The analogy of the mechanism of hæmolysis in blackwater fever and in paroxysmal hæmoglobinuria—diseases which closely resemble each other in their general symptoms—has attracted a considerable amount of attention. It has been found that if the blood of a case of paroxysmal hæmoglobinuria be withdrawn and the serum separated, then cooled to freezing-point, and subsequently warmed to 37° C. with the addition of the patient's erythrocytes, an active hæmolysis takes place. This does not occur in blackwater-fever cases. The test by which this fact is brought out is known as Yorke's autolytic reaction.¹

The theoretical considerations which underlie this reaction are very complicated, and concern the mechanism of immunity, the proportion of hypothetical substances known as the immune body and as complement. In the serum of paroxysmal hæmoglobinuria² the immune body is greatly in excess of the complement, whereas in blackwater fever the reverse obtains.

Symptoms of blackwater fever.—It is doubtful whether one can speak about an incubation period in blackwater fever, but it has been noted in Central Africa that an attack may occur eight days after exposure to malaria, and Arkwright and Lepper, in their series of cases, state that the maximal interval between the first recognized attack of malaria and the first attack of blackwater fever was ten years (in one case), and that the minimal period recorded was fifty days.

Some clinicians recognize a clinical condition which, for want of a better term, may be described as a *pre-blackwater state*. In the Editor's experience this is a most definite condition, and may be recognized by the following clinical signs. The patient is one who

¹ (1) Blood placed in incubator at 37° C. at once; no hæmolysis. (2) Serum kept at 0° C. for 5–7 mins., then in incubator for an hour with erythrocytes; hæmolysis. (3) Serum kept at 0° C. for an hour, then in incubator with erythrocytes; little hæmolysis.

² Donath and Landsteiner have shown that in this disease hæmolysis takes place in the peripheral blood and that cold is the exciting cause.



- 1
2
3
4
- Fig. 1.—At acute stage, methæmoglobin and oxyhæmoglobin.
 Fig. 2.—Stage of defervescence, preponderance of oxyhæmo-
 globin.
 Fig. 3.—Further defervescence.
 Fig. 4.—Stage of recovery, traces of methæmoglobin.

BLACKWATER-FEVER URINE.

(By permission of London School of Hygiene and Tropical Medicine.)

has passed through several slight attacks of fever, or at any rate has been infected with the subtertian parasite for several months. The complexion is sallow, the conjunctiva icteric, the liver enlarged, congested and tender, the tongue furred, the spleen generally enlarged, and constipation is the rule. Persistent headache is usually complained of. The urine is dark, due to the excretion of urobilin, and contains a slight amount of albumin. On examination of the blood, scanty ring-forms of the parasite may be found, but it is a noteworthy fact that cases of subtertian malaria with high fever and large numbers of parasites in the peripheral blood do not, as a rule, develop blackwater.

The *onset* of blackwater fever is usually sudden. A slight or, more generally, a very severe rigor is followed by intermitting, or remitting, or irregular fever with marked bilious symptoms. The pyrexia and rigors do not seem to be the effects of the malaria parasites as much as of the sudden liberation of the products of hæmolysis. In other words, it is a kind of "protein shock." Earlier or later in the attack, usually during rigor, the patient becomes conscious of aching pain—perhaps severe—in the loins, in the region of the liver and spleen, which are enlarged and palpable, and over the bladder. In exceptional instances these local pains are absent. In consequence of a somewhat urgent desire he passes water, when he is astonished to see that his urine has become very dark in colour, perhaps malaga-coloured or, possibly, almost black. The fever continues, though it is not necessarily very high. Very likely he suffers from epigastric pain and distress, bilious vomiting to an unusual extent and, it may be, bilious diarrhœa ; or he may be constipated. The pain in the loins and the liver-ache continue, and the urine becomes darker and darker. By and by the sufferer breaks into a profuse sweat, and the fever gradually subsides. The urine, which hitherto may have been very abundant, or perhaps somewhat scanty, now flows freely ; and after passing through various paling shades, from dark brown to sherry red, becomes once more natural in appearance (Plate VIII). Usually, and coincidently with the appearance of the dark colour in the urine, or even before this has been remarked, the skin and scleræ rapidly acquire a deep saffron-yellow tint. This icteric condition persists and even deepens during the progress of the fever, continuing for several days to be a striking feature in the symptoms. Occasionally bile-pigments are present in the serum ; more usually free hæmoglobin can be demonstrated spectroscopically (Arkwright). When the fever subsides the patient is conscious of a feeling of intense weakness, from which he recovers

but slowly. Fever, with or without rigor, may recur next day, or for several days; or it may cease; or it may be remittent, or almost continued, in type. The hæmoglobinuria may recur with each rise of temperature, or there may be only one or two outbursts; it may continue for an hour or two only, or it may persist, off and on, for several days or even weeks.

In the more severe form of hæmoglobinuric fever there is usually a very great amount of bilious vomiting, of intense epigastric distress, and of severe liver- and loin-ache. The urine may continue copious and very dark in colour; or, continuing hæmoglobinous, it may gradually get more and more scanty, acquiring a gummy consistence, a few drops only being passed at a time. It is considered that the kidneys may excrete up to 36 per cent. of the total hæmoglobin in the blood, though this by no means represents the total amount liberated in many cases of blackwater fever. Finally, urinary excretion may be completely suppressed.

In severe cases death is the rule. It appears to be brought about in one of three or four ways. The fever may assume the typho-adynamic type; or suddenly-developed cerebral, hyperpyrexial, or algid symptoms may supervene. Hiccough is a fatal symptom. In other cases the symptoms may be like those consequent on sudden and profuse hæmorrhage—jactitation, sweating, sighing, syncope. Death may take place from sudden heart-failure after slight exertion, or from exhaustion consequent upon cyclical vomiting, or from sudden hæmorrhage from stomach or bowel. Or it may be that suppression of urine, persisting for several days, terminates, as cases of suppression usually do, in sudden syncope, or convulsions and coma. More rarely, nephritis may ensue and the patient die from uræmic trouble three or four weeks after all signs of hæmoglobinuria and fever have disappeared. Some superimposed infection, streptococcal, septicæmic, or pneumonic, may ensue and be the cause of death some weeks after apparent recovery. One attack of blackwater appears to predispose the individual to a second, and second attacks, or more than two, have been noted in Nigeria in about 20 per cent. of cases; according to Stephens, sixteen is the largest number recorded. It is necessary to lay special stress on these points, for when a man has suffered and recovered from two attacks, the third is generally fatal.

The urine.—If the characteristic dark-brown, generally acid, urine of a hæmoglobinuric case be stood for some time in a urine glass, it will separate into two well-marked layers; an upper of a clear though very dark port-wine tint, and a lower—perhaps amounting to one-half or one-third of the entire bulk—of a some-

what brownish-grey colour, and consisting of a sediment in which an enormous number of hyaline and hæmoglobin tube-casts are to be found, together with a large quantity of brownish granular material. Epithelium is also met with. Blood-corpuscles may be entirely absent, or very few in number. With the hæmoglobin there is also an escape of the serum-globulin of the blood, for the urine, in many cases, turns almost solid on boiling. The precipitated albumin carries down with it as it subsides the dissolved and suspended hæmoglobin, leaving a pale-yellow supernatant urine. For some days after the urine has regained a normal appearance it will still contain albumin, though in gradually diminishing amount. Spectroscopic examination gives the characteristic bands of oxy-hæmoglobin, as well as those of methæmoglobin. The appearance of oxyhæmoglobin is usual in very severe or fatal cases, methæmoglobin in the less severe or mild, in which the prognosis is more favourable. After the disappearance of the blood-pigments, urobilin can usually be demonstrated in pathological amounts.

Mortality.—This varies greatly in different epidemics, in the same and in different places, and under the same treatment. Some cases are so mild and transient, amounting, perhaps, to a single emission of hæmoglobinous urine, with little or no fever, that they are unattended with risk; on the other hand, a practitioner may encounter a run of severe cases in which nearly all die. Some old residents in Africa have passed through ten or more attacks with impunity. In Southern Nigeria and in Algeria the case-mortality has been as high as 50 per cent., but, as a general average, it may be put down as about 25 per cent.

NOTE.—The reader is referred to the monograph of J. Gordon Thomson on Blackwater Fever in Southern Rhodesia, in the Research Memoir Series, Vol. VI, London School of Tropical Medicine, for the most complete summary of our knowledge of this subject.

MALARIAL CACHEXIA

Malarial cachexia is the term applied to a group of conditions, more or less chronic, believed to be the result of an antecedent attack of severe malarial fever, or of a succession of such attacks, or of prolonged exposure to malarial influences.

The leading symptoms are those of anæmia, characterized by the peculiar sallowness of the skin, yellow sclerotics, enlargement of the spleen and, it may be, of the liver as well. As a rule, the subjects of cachexia are liable to frequent and irregular attacks of fever, though in highly malarious countries it is not unusual to see cases in which fever has never been a feature, or it may have been very mild in character. In such countries a large proportion

of the population have enormously enlarged spleens, causing great protrusion of the abdomen, together with much emaciation and dry, rough skins. It is said that in some intensely malarial countries children are occasionally born with enlarged spleens; in rare instances they are infected through the mother in utero, but it is probable that in most cases they become inoculated with parasites immediately after birth.

In the young the general growth of the body is stunted and puberty retarded, and abortion and sterility are common effects of malarial cachexia in adults.

It would seem that the body can become accustomed to the fever-producing toxin of the malaria parasite, much in the same way as it may become accustomed to opium and many other organic poisons, so that a benign tertian parasite, for instance, can undergo a rhythmical development in the blood without the production of an ague attack or other subjective symptoms (see p. 34).

A variety of functional troubles, often observing a curious periodicity, is met with in malarial cachectics; thus one may observe quotidian or tertian neuralgias, gastralgias, vomiting, headaches, tachycardia, and so forth.

There is considerable doubt whether a peripheral neuritis of malarial origin exists. Undoubtedly, well-marked neuritis is met with in certain patients, especially from the West Coast of Africa, though it is possible that cachectic and anæmic subjects are much more prone to contract specific infections of all kinds, of which peripheral neuritis may be one.

Herpetic eruptions are very common in malarial cachectics, and so are hæmorrhages of various kinds. In such patients trifling operations—a tooth extraction, for instance—may prove to be dangerous. Subjects of a malarial cachexia are liable to suffer from intestinal irregularities of all kinds, and are found to be especially prone to secondary infections, such as tuberculosis and dysthenery.

The spleen may become so enlarged under repeated attacks of the congestion attending a succession of fever fits, or in consequence of a less active and perhaps feverless hæmolytic process, that it may come to weigh many pounds, and so to increase in bulk as to occupy nearly the entire abdomen. The capsule of the gland, particularly on its convex surface, is thickened, and perhaps the seat of fibrous patches, or even of adhesions to neighbouring organs. Many of the trabeculæ forming the framework of the gland become greatly hypertrophied. On section, the tissues of such a spleen are found to be moderately firm, and usually of a reddish-brown colour; but when death happens soon after or during a febrile attack, section of the gland

shows a dark surface from deposit of hæmozoin, the pulp at the same time being softened. Perhaps from over-distension, some of the vessels in the interior of the gland give way, and then there is a breaking-down of the spleen pulp in patches, the remains of splenic tissue floating about in the extravasated blood.

“ Splenic index.”—There are practical points in connexion with malarial spleen which deserve mention. The relative absence, or prevalence, of these enlarged spleens or “ague cakes” in the native population is an excellent rough indication of the salubrity or the reverse, as regards malaria, of any particular district. Wherever they are common the district is malarious, and therefore unhealthy, perhaps to Europeans deadly, and should be looked upon as extremely unfavourable for either camping or residential purposes.

Another practical point is that these enlarged spleens are easily ruptured by a blow on the belly ; this fact must be remembered in administering even mild corporal punishment to natives of malarious countries. Splenic ruptures are, of course, unless immediately operated on, generally fatal. Occasionally the spleen may rupture spontaneously owing to rapid increase in size in the course of an attack of fever ; but splenectomy does not necessarily eradicate the malarial infection from the body.

In estimating the amount of malaria in a community the “splenic index” has been found to be most reliable. In other words, children between the ages of two and ten form the only safe guide (Stephens and Christophers), for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion. The infantile spleen rate *per cent.* is the basis of the endemic malariousness of a locality.

The degree of splenic enlargement may be measured with the child standing up or lying down. Considerable differences in the results obtained are given by the two methods, higher values being obtained in the recumbent position. In India and in the tropics generally where gross degrees of enlargement are commonly encountered, the standing position is nearly always used. The best method is for the child to be drawn gently across the observer's knee while the hand is inserted beneath the scanty clothing and pressed against the costal margin while the child is told to take a deep breath. The degree of splenic enlargement is usually classified in finger-breadths below the costal margin. Obviously this method is liable to fallacies. The distance from the costal arch to the pubis is very different in an infant of two years and a child of ten. To overcome this, Christophers has devised a method by applying to the actual measurement from the costal margin to the apex of the enlarged spleen, a correction based upon the nipple-umbilicus length of the child.

In the average Indian child of six years of age the four-finger spleen

reaches to the level of the umbilicus. In malaria surveys, especially when carried out in India, the following rough classification is generally adopted:

Spleen-rate greater than 50 per cent.=Hyperendemic.

Spleen-rate 25 per cent. to 50 per cent.=Highly endemic.

Spleen-rate 10 per cent. to 25 per cent.=Moderately endemic.

Spleen-rate less than 10 per cent.=Healthy.

The child spleen-rate gives the measure of endemicity, the average enlargement that of intensity.

The *parasite index* is a simple percentage figure calculated from the number of persons actually showing parasites in the peripheral blood at the time of examination. Figures for children and adults should be kept separate, as the spleen-rate falls with age more rapidly than does the parasite-rate which shows how many adults of a community are really "healthy carriers."

The parasite-rate should always be obtained from the study of thick as well as thin films. From a study of curves prepared from splenic and parasite *indices* according to age, it is found that they run parallel to a remarkable degree. The parasite index as a sign of infectivity is more reliable up to five years of age, after which to the age of twenty-five it is on an average 10 per cent. less reliable than is the splenic index.

Changes in the liver.—Like the spleen, the liver in malarial cachectics becomes enlarged during accessions of fever. Under the influence of a succession of acute attacks, hepatic congestion may gradually acquire a more or less permanent character.

It is in livers of this description that a form of what is called *siderosis* is produced—a condition resulting from chemical changes undergone by the yellow pigment with which the various cells of the organ are charged. When first deposited, this pigment gives no ferrous reaction with ammonium sulphide, or with the double cyanide of iron and potassium; as the deposit becomes older, chemical changes ensue, resulting in the elaboration of a form of iron which will then yield the characteristic black colour with the former, and blue colour with the latter reagent.

Certain clinical facts about malarial hepatic congestion and hepatitis are of importance. In the first place, such conditions do not tend to terminate in suppuration; in the second, they are almost invariably associated with splenic enlargement. These are important facts to recollect when it becomes a question of the diagnosis of malarial hepatitis from abscess of the liver. Another important fact to remember is that recent malarial enlargement of the liver is usually curable, depending, as a rule, on simple congestion; whereas old-standing malarial hepatic enlargement is

usually incurable, depending, as it usually does, on hypertrophy of the connective tissue and a cirrhotic condition of the organ.

Changes in the kidneys and the heart.—Changes similar to those found in the liver in the course, and in consequence, of malarial disease occur in the kidney; in time they result in confirmed Bright's disease; especially is this true in quartan infections. Hence, probably, the frequency of Bright's disease in some highly malarious climates. As a consequence of defective nutrition from prolonged anæmia and recurring fever, the muscular tissue of the heart in chronic malarials may degenerate, the ventricles dilate, and, in time, the lower extremities become œdematous. For the same reason the subjects of valvular affections of the heart, whether compensated or otherwise, must be regarded as unsuitable for residence in malarial countries.

PATHOLOGY OF MALARIA

The blood.—As the malaria parasite is a blood parasite, we naturally expect that the primary effect of its presence will be exercised on, and manifested in, the blood; and as the parasite lives in and at the expense of the corpuscles, destroying a certain proportion of them—in fact, all those attacked—we look, in the first instance, for a corresponding diminution in the number of the corpuscles—an oligocythæmia. In order to produce symptoms, it is estimated that there must be at least one parasite to every 100,000 red cells.

The reduction of the red cells in malaria cannot be accounted for by the proportion of the red blood-corpuscles attacked or directly consumed by the parasite. The amount of hæmolysis actually produced by the mechanical action of the parasites should be easily compensated by the latent physiological hæmogenic margin, but this is not the case.

Often, after a single paroxysm of some pernicious malarial fever, as many as half-a-million or even one million corpuscles per c.mm. drop out of the normal five millions; and this reduction may go on, as paroxysm follows paroxysm, until the corpuscular richness has fallen to one million, or even less. Malarial oligocythæmia is accompanied by changes in the red cells themselves, such as poikilocytosis, anisocytosis, basophilic stippling, and other signs of degeneration of the red cells. (*See Appendix, p. 861.*)

In addition to the destruction of the red cells, there is a marked hæmoglobin diminution of the surviving corpuscles to 50, 20, or even 10 per cent. Consequent upon this there is a diminution of the total hæmoglobin-content to an even greater degree.

On the whole, in malaria, as in most anæmic conditions, the corpuscles are larger than normal—particularly those attacked by the parasite, especially the benign tertian. Occasionally we come across genuine megalocytes and, not infrequently, certain very minute dark-coloured, spherical corpuscles, which may be nucleated and of embryonic type. Erythrocytes with basophilic stippling are not uncommon, and until recently most pathologists regarded these basophilic granules as evidence of the degeneration of the erythrocytes.

The blood sugar is decreased during the course of malaria fever; this may be a matter of the glucose-content of the blood which is known to be essential for the well-being of the malaria parasite.

In all malarial conditions of considerable standing there is a marked diminution in the volume of the blood; we do not, therefore, at the post-mortem examination find that congestion of the organs which is so marked a feature of most specific fevers.

Leucocytes in malaria.—The work of many observers tends to show that the leucocytes are increased during the actual malarial paroxysm. Within a few hours of the onset of the attack the total leucocyte-count has fallen to 3,000–5,000 per c.mm., and the ratio of white corpuscles to red, changes from the normal 1 : 500 to perhaps 1 : 900. There may, however, be an increase of the leucocytes, especially in subtertian infections of the pernicious type associated with intestinal symptoms. The diminution in the number of leucocytes is not so pronounced and does not last so long as in kala-azar. Together with the leucopenia there is a relative increase in the mononuclear cells. D. Thomson has shown that the percentage of large mononuclear leucocytes estimated hourly during an attack of malaria gives a curve which is exactly the reverse of the temperature chart; during the rigor and at the height of the fever the percentage is at its lowest; during the afebrile period it rises again. The increase in the large mononuclear cells may persist for weeks after the patient has seemingly been cured by quinine. Stephens and Christophers have stated that a mononucleosis of 15 per cent. (in the absence of kala-azar) is diagnostic of malaria. The count is not usually above 20 per cent. A history of fever with a relative leucopenia and an increase of the large hyaline mononuclear cells up to 15 per cent. is strong confirmatory evidence of malaria.

A leucocytosis *per se* does not necessarily exclude malaria.

Phagocytosis.—The hæmozoin, the detritus of the parasites and red blood-corpuscles, is taken up by the polymorphonuclear

leucocytes and large hyaline macrophage cells. A considerable destruction of red blood-corpuscles, both normal and containing parasites, takes place in the spleen, and this process of blood destruction is considered to be one of the principal causes of malarial anæmia. The large number of pigmented macrophage cells in the splenic sinuses is a striking feature of the pathology of subtertian malaria. The finding of pigment-containing leucocytes is proof that the patient is infected with malaria. The observer must convince himself that it is true hæmozoin and not dust or dirt on the film. As a rule, when pigment is present within a large mononuclear cell, there is a good deal of it and it is either yellowish-brown or brown-black.

Macroscopic morbid anatomy.—The *spleen* is enlarged—often very much enlarged; its surface is dark—black sometimes—what is called pigmented. On section, the gland tissue is also found to be dark. Generally the parenchyma of the organ is so much softened as to be almost diffuent, so that the tarry pulp can sometimes be washed away by a quite gentle stream of water. In acute and rapidly fatal cases of subtertian malaria the capsule is stretched almost to bursting-point, and resembles a bladder distended with congealed blood. The *liver*, too, is softened, congested, enlarged, and pigmented, and of an olive-brown colour. The vessels of the *pia mater* and *brain cortex* are full, and the grey matter may present a peculiar leaden hue. In fatal subtertian cases of the cerebral type, punctiform hæmorrhages are present in the white matter of the brain, especially in the corpus callosum. These lesions are probably due to the blockage of the blood-vessels by the sporulating parasites. Margulis, Thomson and Seyfarth have described malarial granulomata, or focal degenerations (Fig. 20), which are direct results of these hæmorrhages. In microscopical appearances they somewhat resemble tubercles and they are formed of the conglomeration of glia cells round the centre of degeneration. Possibly this grave alteration in the structure of the cerebral cortex may be responsible for the various mental and nervous symptoms which frequently ensue after an attack of cerebral malaria. The *marrow* of the spongy bones, such as the sternum and the bodies of the vertebrae, is also dark and congested; and a similar state of pigmentation and perhaps congestion may be discovered in the *lungs*, *alimentary canal*, and *kidneys*. In fatal subtertian cases these organs are specially affected, a general parenchymatous degeneration with special incidence on the epithelium of the tubules being present.

Malarial pigmentation may be found in blood from any of the

organs previously mentioned, within the endothelial cells of the arterioles and capillaries, as minute grains or actual blocks; it may be aggregated so as to form veritable thrombi and occlude vessels (Plate VII, Fig. 2). In the solid organ the pigment, as well as developmental and segmenting forms of the subtertian parasite, is often found ingested by inflammatory macrophage endothelial cells. Particularly is this the case with the spleen and bone-marrow; often, too, with the brain liver, epiploon, and intestinal mucosa. The spleen and bone-marrow are further distinguished from the other organs mentioned by the position in which the

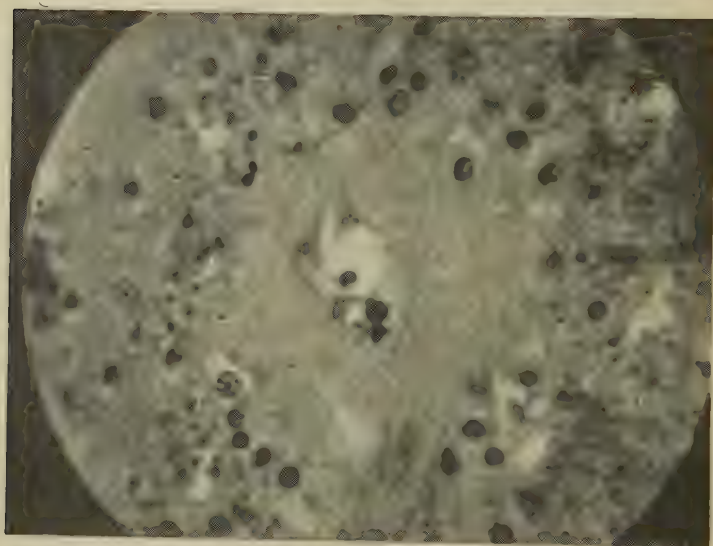


Fig. 20. Section of granuloma of brain in subtertian malaria. $\times 100$.
Showing "focal degeneration." (Thomson and Annecke.)

hemorizin occurs in them. In all organs the pigment is found in the blood-vessels, but only in these two is it found in the cells of the parenchyma as well, and outside and away from the blood-vessels. In the liver it is found in the interstitial or Küpfer cells.

Nature and source of malarial pigment.—The pigment is identical with that formed within the malaria parasites, and is insoluble even in strong acids; it is altered by potash and is entirely and rapidly dissolved by ammonium sulphide. In recent infections it occurs as minute dust-like grains; in infections of some standing as coarser particles, or as agglomerations of these into irregular, mammillated

lumps. It is an iron-containing derivative of hæmoglobin which is primarily split up into a proteid globin and a pigment—hæmatin, and it is from the latter that hæmozoin is derived. This pigment in the solid organs is apparently carried to these situations by the large mononuclear, and even by the polymorphonuclear leucocytes; one can sometimes observe the ingestion of this material in fresh preparations made from the peripheral blood. So far as the circulation is concerned, such a pigment is found in no other disease whatever. As an extravascular pathological product a similar pigment is found in schistosomiasis and certain melanotic tumours; but only in the cells of the tumour, never in the blood-vessels.

Of all the vessels of the body, the splenic vein is that in which malarial pigment is most abundant. Whereas in other vessels it is found to be included in ordinary leucocytes, in this vessel it is included in large white cells, probably identical with splenic pulp cells. The reason for this is that the spleen is not only the physiological destination of the hæmozoin-laden leucocytes, but is also a favourite nursery of the parasite.

Besides the pathognomonic hæmozoin, there is usually found in the organs a considerable amount of a yellow or brown pigment, *hæmosiderin*. This pigment is found not only in the capillaries, but also in the parenchyma cells of the liver, spleen, pancreas, and kidney, as well as in the bone-marrow and the connective tissues. It is by no means characteristic of malaria, but occurs in all diseases in which there is an extensive breaking up of red blood-corpuscles, as in paroxysmal hæmoglobinuria, in pernicious anæmia, in organic poisonings, etc. Contrary to what has been said about hæmozoin, it is equally insoluble in acids, alkalis, and alcohol.

Apparently, under the name of hæmosiderin two pigments have been included, one containing iron, the other not; the latter is known as *hæmofuscin*, though some authorities consider that there is originally one pigment which, after deposition, breaks up into free iron and the iron-free hæmofuscin. The ferruginous granules are more abundant after an active hæmolysis, and can be demonstrated by the potassium ferrocyanide method, in which they show up blue; the hæmozoin (in which the iron is firmly combined) shows up black, while the hæmofuscin remains yellow. In a more protracted hæmolysis, as in chronic malarial cachexia, the yellow pigment alone is found.

Polycholia.—Up to a certain degree of pathological hæmoglobinæmia the liver can deal with the free hæmoglobin; and so it comes about that when this substance is free in the blood, the

secretion and flow of bile become correspondingly increased. If this flow of bile be excessive it gives rise to what are called "bilious symptoms"—bilious vomiting, bilious diarrhœa—symptoms which are so common in malarial disease, particularly in the variety known as "bilious remittent." Thus, polycholia is a constant and often urgent feature in most malarial fevers, and is good evidence that in malarial infections there is a surcharge of the blood with free hæmoglobin. It is not improbable, although this point is disputed, that the yellowness of the skin and scleræ observed in these fevers is due to tinting of the tissues by the liberated hæmoglobin, and not, as is popularly believed, to biliousness or cholæmia from bile absorption (*see* p. 48).

Enlargement of the liver.—In all three types of malaria, enlargement of the liver is apt to occur. In life it is usually accompanied by tenderness of the organ and slight changes. The pathological appearances are due to pigmentation and great congestion; the capillaries themselves may be distended with macrophage cells, endothelial cells, and malarial pigment. The liver cells are usually atrophied and contain much hæmofuscin, while the hæmozoin is found in the interstitial or Küpffer cells. In subtertian malaria there may be extensive fatty degeneration of the liver cells.

The heart.—In rapidly fatal cases of subtertian malaria Dudgeon and Clarke have found a diffuse fatty degeneration of the heart similar to that occurring in acute diphtheritic poisoning, while Gaskell has observed the actual presence of the subtertian parasite within the cardiac cells. The recognition of these changes in the heart goes far to explain the dramatically sudden deaths which may occur in subtertian infections.

The suprarenal glands.—In subtertian infections a constant lesion has been noticed in these glands, especially in the reduction of the lipoids of the cortex. It has been thought that these changes explain a syndrome occasionally met with in subtertian fever, characterized by great muscular weakness and low blood-pressure.

PATHOLOGY OF BLACKWATER FEVER

The microscopic pathology of blackwater fever resembles very closely the pathology of subtertian malaria, already described.

The *gall-bladder* is filled with dark-green viscid bile. The spleen contains a large amount of hæmozoin, together with evidence of phagocytosis of the red blood-corpuscles by the leucocytes and endothelial cells (hæmatophagy).

The *kidneys* are enlarged and congested, and of a peculiar sandalwood or greyish-violet-brown colour, the tubules being blocked with hæmoglobin infarcts, and the cells of the collecting tubules laden with hæmofuscin, while in the capillaries a considerable amount of hæmozoin will be found. The blockage of the kidney tubules is attributable, apparently, to two causes:

the hyaline or blood-casts, as they are called, are due to the coagulation of highly albuminous hæmoglobin-containing serum, while the cellular casts are formed by dislodged and degenerate epithelial cells of the urinary tubules which, when impregnated with hæmoglobin, collect in the lumen of the tubules. In more chronic cases of the disease the appearances of the kidney are different. Should the patient then die of uræmia, the macroscopic and microscopic appearances of the kidney are those of a chronic parenchymatous degeneration. The *bone-marrow* is brown and of a fluid consistency.

In the early stages of blackwater fever the *blood* shows a great reduction in the number of red blood-corpuscles, but very little other change; the degree of reduction depends upon the extent of the hæmolysis. If it is very extensive, the red blood-corpuscles may fall to 1 million per c.mm. within 24 hours, but in fulminating cases counts of 500,000 have been recorded. At this stage free "shadow" corpuscles can be seen in fresh blood preparations, and it is said that effete red cells may occasionally be found enclosed in the phagocytes. During the stage of recovery the most striking microscopical changes seen are the intense polychromasia and polychromatophilic stippling of the red blood-corpuscles. According to the recent teaching, both these changes are held to be indicative of blood regeneration, and, as evidence of this, nucleated red blood-corpuscles may make their appearance; at the same time, as a rule, a definite increase of the mononuclear cells above 12 per cent. can be substantiated; but, save in the absence of malaria parasites, there is no striking feature in which the blood picture differs from that of a pernicious case of subtertian malaria.

DIAGNOSIS OF THE THREE CLINICAL VARIETIES OF MALARIA

The recognition of the various forms of malaria parasite in the peripheral blood entails a knowledge of blood examination. For the details of this and of the methods of staining the blood the reader is referred to the Appendix, p. 859. As a general rule, the beginner should work with unstained preparations of fresh blood only. He will then be able to appreciate the various changes that take place in the malaria parasite at different stages of its existence, and also the appearances of the hæmozoin.

On examining successful slides prepared by any of the Romanowsky methods, the body of the malarial parasite is stained blue, and the chromatin of the nuclei ruby-red; and in deeply stained preparations of the tertian parasite the hæmoglobin of the including red blood-corpuscles will be dotted over with the fine or coarse red granules known as Schüffner's dots.

The paucity of parasites in the peripheral blood does not necessarily indicate that the infection is a slight one, or that the patient's condition is not dangerous; this is especially so in cerebral cases of subtertian infection. Some workers prefer the thick-drop method (Appendix, p. 857) as offering a more certain chance of discovering the parasites when they are scanty in the peripheral blood.

Bearing of quinine on microscopical diagnosis.—It is of little use to examine the blood for the intracorpuseular forms of the malaria parasite after full doses of quinine have been taken; the drug rapidly brings about the disappearance of this phase of the parasite. The crescent, or gametocyte, of the subtertian parasite, alone, is unaffected by quinine, and in suitable cases may be found for weeks after the patient is cinchonized; on the other hand plasmoquine has a selective action on this form (*see* p. 77).

In performing routine examinations for malaria, it is most necessary to insist that the blood-film be taken before full doses of quinine are given. The diagnosis of malaria after exhibition of quinine, or in the latent stages of the infection, always presents great difficulties. The discovery of pigmented leucocytes—that is to say, leucocytes containing grains of hæmozoin—which appear in the peripheral blood shortly after an attack of fever, may be taken as absolute evidence of recent malaria. Formerly, importance was attributed to the rise in the number of the large mononuclear cells which takes place in the blood-stream after an attack of fever, but there are fallacies attached to this (*see* Appendix, p. 861). To be of much value, both the total and the differential leucocyte-counts must be carried out, for during the actual fever, especially in subtertian infections, while the temperature is rising, a definite leucocytosis takes place, and this will naturally affect the differential leucocyte-count to a very considerable degree. A definite increase in the number of the large mononuclear cells, above 12 per cent., is certainly suggestive of a malarial infection, especially if they are of the macrophagocytic type, possibly derived from the vascular endothelium.

Gordon Thomson and others have suggested that a complement-deviation test, using an emulsion of an organ rich in parasites, as well as artificial cultures of the plasmodia as antigens, may prove to be a distinct aid to diagnosis.

About 28 per cent. of malarial bloods in the acute stage of the disease, when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction (Fairley); but this is not so in either the chronic or the quiescent stage, a fact which has to be borne in mind in excluding syphilis in a malarial subject.

Diagnosis of malaria by the therapeutic action of quinine.—It is unfortunately true that, in countries where malaria exists, any case of fever is diagnosed as such, and the practitioner may be called in only when a considerable amount of quinine has been taken and has failed to achieve the desired results. Unfortunately,

too, a good many practitioners are in the habit of relying unduly upon the therapeutic action of quinine, without verifying their diagnosis by microscopic examination.

Diagnosis from clinical signs.—The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections; in the subtertian infections, however, the fever may be most irregular, and there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity ("ague cake"), but in early, and it may be very severe, infections the spleen may not be sensibly enlarged at all, and it therefore fails as a clinical guide. Moreover, the patient may be suffering from some totally different kind of fever, and the palpable spleen may be the result of a long-standing infection quite unconnected with the present attack.

Diagnosis by the patient's history.—A suddenly developed fever arising in a previously healthy person who has recently arrived from a malarious country usually turns out to be a case of malaria fever. In instances of this kind the patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for, occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the cold, may run a very severe course; this is especially the case with recent arrivals from the West Coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite in both cases having lain dormant in the blood-stream, it may be as long as eight months.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. *Tertian and quartan periodicity occur only in malarial disease.*

Diagnosis by splenic puncture.—According to Knowles, Acton, and das Gupta, the spleen appears to function as the grave rather than the birthplace of the malaria parasite; therefore spleen puncture may, exceptionally, be used as a method of diagnosis especially in chronic and relapsing cases due to the benign tertian parasite. In films from such a puncture the observer sees

malarial pigment, both free and intracorpuseular, and remains of malaria parasites undergoing disintegration.

Provocative methods of diagnosis.—It has been noted, particularly by Italian observers, that exposure to undue fatigue or cold is apt to bring on an acute attack of malaria fever in latent cases, thus rendering the detection of the parasites in the peripheral blood comparatively easy. It is suggested by some, though to others it may not appear justifiable, that a patient in whom malaria is suspected should be made to climb a high mountain and expose himself to cold at a considerable altitude, in order to provoke an attack.

There are other methods which have been employed in order to cause the parasites to appear in the peripheral blood; such are the subcutaneous or muscular injection of normal serum or other substances producing protein-shock, with strychnine, nitroglycerine, iron, ergotin, pituitary extract or adrenalin. The intravenous injection of salvarsan is sometimes followed by a similar result. X-rays applied to the spleen, and ice-packs to the abdomen, are other provocative methods. It is said that the most efficacious measure is the intravenous injection of 2 c.c. of adrenalin hydrochloride dissolved in 300 c.c. of normal saline, and that this procedure results in the immediate reduction of an enlarged spleen, with the appearance of the parasites in the peripheral blood.

DIFFERENTIAL DIAGNOSIS OF MALARIA AND OF BLACKWATER FEVER

The tendency to regard and diagnose all fevers occurring in tropical countries, or in individuals who have returned from tropical countries, as malarial, has already been noted. The opposite error of overlooking malarial infection must be equally guarded against. In many tropical and subtropical localities practically every European is, or may be, the subject of active or latent malaria. The tropical practitioner, therefore, should approach the diagnosis of all his cases with the idea ever present to his mind that they may be malarial, or complicated with malaria.

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical in origin; but there is one point to be borne in mind, for which there seems to exist at present no adequate scientific explanation, namely, that in patients who have suffered for some time from recurrent malarial attacks, the temperature of a subsequently contracted febrile disease, for example measles, may show a periodicity foreign to its usual character.

Diagnosis of malaria from liver abscess.—In hepatic abscess, although the liver is enlarged, the spleen is not necessarily so; splenic enlargement, though an occasional, is not a usual feature in liver abscess. In hepatic abscess the fever occurs generally, though not invariably, in the late afternoon or evening; the patient may perspire profusely, independently of fever lysis, at any time

of the day or night—very generally whenever he chances to fall asleep.

Diagnosis of bilious remittent malaria from yellow fever.—In bilious remittent the icteric tinting of the skin is an earlier feature; albuminuria is not so common and generally not marked; temperature is maintained high for many days, not subsiding in three or four days as in yellow fever; the vomiting is profuse and bilious; the pulse does not become phenomenally slow as in yellow fever; in the initial stage the eyes are not congested to the same degree; and the parasite is to be found in the blood.

Diagnosis of malaria from typhoid and paratyphoid fevers.—Without the microscope it is sometimes impossible to diagnose typhoid types of malarial fever from genuine enteric. In both fevers there may be diarrhoea or constipation; in both, splenic enlargement; in both, typhoid tongue, delirium, and the entire range of typhoid symptoms.

Diagnosis of malaria from other types of paroxysmal fever.—The following, also, are often mistaken for malarial fever: Cerebro-spinal meningitis; fever of urinary origin; the fever attending the passage of gall-stones, or inflammation of the gall-bladder; that associated with pyelitis and surgical kidney; perineal abscess; lymphangitis, particularly that form associated with elephantiasis and other filarial diseases; undulant fever; relapsing fever; trypanosomiasis; kala-azar, generally an irregular fever, though often quotidian, and almost invariably accompanied by enlarged liver and spleen and by anæmia; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anæmia, with splenic leucocythæmia, with visceral syphilis, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions. The use of the microscope must not be neglected in such cases if there be the slightest doubt as to their exact nature. Malaria may, of course, complicate other diseases.

Differential diagnosis of special forms of subtertian malaria.—As has already been indicated, there is a natural tendency for medical men unacquainted with the clinical forms which subtertian malaria may assume, to diagnose its various symptoms as manifestations of some other disease. Even surgical conditions, such, for example, as appendicitis or other acute abdominal disorders calling for urgent operative interference, may be suspected. The following statement is based upon actual diagnoses which have been made on clinical grounds alone, without the confirmation of a microscopic examination, but which subsequently proved to be cases of subtertian malaria:—

- (a) *Cerebral forms* of subtertian malaria are apt to be mistaken for sunstroke, heatstroke, mental derangement, hysteria, alcoholism, aphasia, convulsions, epilepsy, cerebro-spinal meningitis, or even plague.
- (b) *Abdominal forms*, for dysentery, both amœbic and bacillary, cholera or paracholera, intestinal obstruction, appendicitis, biliary colic, cholecystitis, hæmorrhagic pancreatitis, or liver abscess.
- (c) *Pulmonary forms*—i.e. malarial pyrexia with pulmonary congestion and myocarditis—for bronchitis, pneumonia, and pleurisy, especially on the left side (due to congestion of spleen), disordered action of the heart or even valvular disease.
- (d) Those with *cutaneous petechiæ*, for measles, endocarditis, or purpura.
- (e) The *febrile cases* with remittent pyrexia, for influenza, rheumatic fever, enteric, phlebotomus fever, trench fever, paratyphoid, or relapsing fever.
- (f) The *icteric cases*, for yellow fever, Weil's disease, or febrile obstructive jaundice.
- (g) The *cachectic cases*, for acute nephritis, pernicious anæmia, splenomedullary leucocythæmia, debility, or pulmonary tuberculosis.
- (h) *Œdematous forms*, exceptional cases with general anasarca, ascites, and polyuria, may be mistaken for beriberi; a general œdema may be the only outstanding sign in a heavy subtertian infection.

Differential diagnosis of blackwater fever.—The diseases with which blackwater fever might be confounded are—(1) paroxysmal hæmoglobinuria; (2) bilious remittent malaria; (3) yellow fever; (4) infectious jaundice. If it be borne in mind that rigor, hæmoglobinuria, pyrexia, are all in evidence at the outset in blackwater fever, and also that blackwater fever is acquired only in certain countries, an error in diagnosis is improbable.

PROGNOSIS OF MALARIA AND OF BLACKWATER FEVER

As a general rule, **malaria** is a much more serious disease in children than in adults, and its attacks are more marked in women than in men. It is a serious disease in the weakly, especially in those whose constitutions are undermined by any intercurrent disease, such as phthisis or dysentery. It may lead to abortion in pregnant women, and the possibility of such an occurrence must always be reckoned with. It assumes a more serious form in times of famine or in war, and in those who are exposed to great physical exertion, especially if they are unable to obtain suitable food. In certain parts of the tropics it is a popular superstition that patients with fever should be starved, and this is frequently a contributory cause of death. As regards the severity of the disease as a whole, it has a distinct relation to the prevalence of the different types, a higher mortality-rate being observed in patients with subtertian infection, although we know that in times of stress so-called benign

malaria may prove fatal in a half-starved population. Finally, in the average healthy European, although the occurrence of repeated relapses may undermine his health, the general expectation of life is not seriously affected.

Prognosis of blackwater fever.—A severe attack of blackwater fever generally rids the patient of his present malaria infection, but, as the result of this very exhausting illness, his general health suffers for some time to come. Patients who have passed through one attack should not be permitted to return, for a year or more, to an endemic centre of the disease. The course of a particular attack can, generally speaking, be judged by the severity of its onset. So far from protecting against future attacks of blackwater fever, the patient appears to be predisposed to the condition. Therefore, those who have survived two attacks should not be permitted to return to the tropics; a third often proves fatal.

Apparently mild cases in which fresh paroxysms occur are of grave import. Anuria indicates a fatal termination.

TREATMENT OF MALARIA

As soon as a diagnosis of malaria has been arrived at, unless there be some very manifest contraindication, the first duty of the practitioner is to set about giving quinine.

Treatment of simple benign tertian or quartan attacks.—During a paroxysm of ordinary intermittent fever it is better, before giving quinine, to wait until the rigor and hot stages are over and the patient is beginning to perspire. When the skin is moist and the temperature begins to fall, the earlier the drug is commenced the better: 10 gr., preferably in solution, should be administered at the commencement of sweating, and thereafter 10 gr. three times a day after meals for the next week, though there appears to be an advantage in giving it, whenever possible, in smaller doses at more frequent intervals—6 doses of 5 gr. each. If the patient is constipated, a saline purge should be administered before the quinine is exhibited. This is an almost certain cure. The quinine may not always prevent the next succeeding fit, but it nearly always diminishes its severity; in ninety-nine cases out of a hundred the second following attack does not develop. At the same time, with a view to prevent recurrence of fever, the patient is directed to take, once a week, a mild saline, sulphate of soda or Carlsbad salts, in the morning, and three 5-gr. doses of quinine during the day, or 15 gr. in one dose. After the first week,

iron and arsenic in pill, tabloid, or solution, such as a 3-gr. tabloid containing iron hypophosphite, arsenious acid, and strychnine, or a mixture containing ferri et ammon. cit. 10 gr., liq. arsenicalis 3 min., and water 1 fl. oz., are prescribed for a fortnight, and, after an interval of a week, for another fortnight. *The weekly aperient and quinine had better be kept up for six weeks or two months or longer.*

The quinine hydrochloride is the form which should be used by preference; it may be obtained in tabloid form, and taken well crushed up in water; the bitter taste is quickly removed by masticating a piece of bread.

Quinine sulphate pills are to be avoided, as they often pass through the intestinal canal without being absorbed. For this reason *sugar-coated tabloids are not recommended for use in the tropics.* When the sulphate is given in solution it must be dissolved in acid; for instance, 2 min. of acid. sulph. dil. to every 10 gr. of the salt.

Methods of disguising taste of quinine.—An agreeable and efficacious method of prescribing quinine is to give it in an effervescent mixture composed of 10 gr. of quinine hydrochloride and citric acid mixed together in liquid form with $\frac{1}{2}$ oz. of water, to which are added 4 gr. of ammonium carbonate and 20 gr. of potassium bicarbonate in powder form. In order to disguise the disagreeable taste of quinine, which is so objectionable to some people, syrup of orange or glycerin (1 dr.) may be added. Quinine is rendered less bitter if dissolved in milk.

Quinine and its derivation.—Quinine is an alkaloid obtained from the bark of different species of cinchona tree; those under cultivation are *C. ledgeriana* (yellow bark), and the red quinine, *C. succirubra*, which is mostly grown in Java, while in India a hybrid between the two is found most satisfactory. Other varieties are *C. pitayensis* and *C. lancifolia*. The trees vary in size up to eighty feet and are clothed in evergreen leaves which in *C. succirubra* are elongated or broadly oval. The flowers are white or pinkish in colour and are arranged in panicles. The cinchona trees are indigenous to the western mountainous regions of South America, flourishing at altitudes between 3,000 and 9,000 feet. As a general rule *C. ledgeriana* contains more quinine than does *C. succirubra*.

The bark of the root, trunk and stems is dried, powdered with lime and damped. After being kept for two days in this condition, the mass is made into a thin paste with water, put into vats with caustic soda and mineral oil, heated to 170°F. and stirred for half-an-hour. After being allowed to settle, the contents are separated into two layers; the oil on top containing the alkaloids, is decanted into separators and mixed with dilute sulphuric acid; the supernatant acid liquor containing quinine, together with the other alkaloids, is drawn into troughs and neutralized. If the bark be that of *C. succirubra*, all the alkaloids it contains are precipitated with caustic

soda to form "cinchona febrifuge." After separation of the pure quinine by a process of centrifugation, the residual alkaloid contains cinchonidine, quinidine and cinchonine.

Dosage of quinine: toxic effects.—There is great difference of opinion and practice about the dose of quinine. Some give 30 gr. at a dose, some give 3 gr. The former is too large a dose for ordinary cases, the latter too small. It must never be lost sight of that occasionally quinine in large doses produces alarming effects; not ringing in the ears and visual disturbances merely, but actual deafness and even amblyopia, both of which may prove very persistent, and occasionally permanent. It may also produce profound cardiac depression and gastric disturbance, and even death from syncope. Urticaria is another, and not very uncommon, effect of even small doses of quinine; some cannot take it on this account, and prefer to endure the disease rather than suffer the intolerable irritation induced by the remedy. Some consider that the addition of hydrobromic acid dil., 10 min. to every 10 gr. of quinine, prevents the tinnitus.

Quinine amblyopia is generally the result of intense quinine poisoning after a dose of 80-160 gr. In exceptional cases, with an idiosyncrasy to the drug, temporary blindness has followed even moderate doses. Other symptoms, such as mental confusion and coma, may accompany the amblyopia.

Quinine in pregnancy.—Care should be exercised in giving quinine to pregnant women, for undoubtedly, if administered in large doses, it may sometimes cause miscarriage. The fact of pregnancy, however, must not debar the use of the drug altogether; only, in such circumstances, it should be given in the minimum dose likely to be effectual, say 3 gr. repeated every eight hours for two days. *A pregnant woman will run more risk of miscarriage and of detriment to her health from repeated ague fits than from a reasonable dose of quinine.*

Quinine in the puerperal state.—It is a wise precaution in malarious countries to give a few 5-gr. doses of quinine during labour or soon after. The puerperal state seems to have the effect, as any other shock or physiological strain might, of waking up the slumbering malaria parasite. A dose or two of quinine in these circumstances does no harm, and may, by choking off a threatening fever, avert suffering and anxiety, and even danger.

For children under one year, $\frac{1}{2}$ -1 gr. for a dose suffices; for older children the dose must be increased proportionately to age and strength. Children tolerate the drug well, so that in serious

cases—pernicious comatose or other cerebral forms—the drug should be vigorously pushed.

If a supposed ague resists the doses of quinine mentioned, the diagnosis should be revised.

Excretion of quinine.—Nierenstein's observations show that the excretion of quinine is the same by whatever route it is administered. The drug appears in the urine within five minutes, and altogether one-tenth of the total quantity is passed in this manner, the highest concentration being 7–11 gr. quinine base per litre. The recognition of the drug in the urine is effected by means of the Mayer-Tanret method: 1.35 gm. of mercuric chloride in 75 c.c. of water is mixed with 5 gm. of potassium iodide in 20 c.c. of water in a 100-c.c. flask, the former being poured into the latter solution under agitation. On addition of the urine a turbidity appears if quinine is present. It is said that it can be detected at all times in the urine of patients taking daily doses of 5 gr. and upwards, and for 70 hours after its administration is stopped. Should albumin be present, it is precipitated by the reagent; the urine should therefore be boiled, and filtered while warm. On cooling, the urine again becomes turbid if quinine is present, and this turbidity disappears on further heating. By matching the opacity with Brown's tubes, the number of grains per ounce can be estimated.

Sinton's alkaline quinine treatment.—Sinton (1923) has advocated a standard treatment for malaria in India. The patient is first given as an aperient, 3 gr. of calomel followed by 1 oz. of magnesium sulphate dissolved in an equal amount of warm water. Should nausea or vomiting be present, the calomel can be given in smaller doses with sodium bicarbonate. Two mixtures are given as follows:

(a) <i>Alkaline mixture.</i>		(b) <i>Quinine mixture.</i>	
Sodium bicarbonate	gr. 60	Quinine sulphate	gr. 10
Sodium citrate	gr. 40	Citric acid	gr. 30
Water . . . to	oz. 1	Magnesium sulphate	gr. 60
		Water . . . to	oz. 1

Treatment is commenced the morning after the case has been microscopically diagnosed. One dose (1 oz.) of the alkaline mixture is given at 7.30 a.m., repeated at 9.30 a.m., and again at 11.30 a.m. Fifteen to thirty minutes after the last dose of alkaline mixture, one dose (1 oz.) of the quinine mixture is given. At 6 p.m. a further dose of the alkaline mixture is given and is followed, fifteen to thirty minutes later, by a second dose of the quinine mixture. For the next five days one dose of the alkaline mixture is given thrice

daily—at 7.30 a.m., 11.30 a.m., and 6 p.m., followed on each occasion by 1 oz. of the quinine mixture, fifteen to thirty minutes after each dose of the alkaline mixture. For the remaining two days of the week, one dose of the alkaline mixture is given morning and afternoon, followed fifteen to thirty minutes later by one dose of the quinine mixture.

In seven days the patient thus receives a total of 180 grains of quinine in solution. In the case of women, or when there is much gastric disturbance, each dose of the alkaline mixture may be replaced by one containing 2 drachms of sodium citrate in 2 oz. of water, taken slowly. If there is much vomiting it may be necessary to give a dose of tincture of opium before treatment. In severe cases of subtertian malaria the amount of sodium bicarbonate in the alkaline mixture may be increased to 90 gr., dissolved in 2 oz. of water. With this treatment Sinton claims that relapses occurred only in 28 per cent. of cases of benign tertian malaria. It is not always possible to carry out the alkaline quinine treatment in its entirety. To replace it the following method is practised in the Calcutta School of Tropical Medicine.

The prescription is as follows :

Quinine sulphate	gr. 10
Pulv. acidi citrici	gr. 20
Magnesium sulphate	gr. 10
Spirit. anisi	℥ 10
Syrup. simplicis aquam	[āā 3 ½

Of this mixture 1 oz.—containing 10 gr. of quinine in solution—is given three times a day, two-and-a-half hours after food, on an empty stomach for one week. The dose is then reduced to 1 oz. taken two-and-a-half hours after food twice a day, and continued for a further two weeks.

Other forms of quinine.—*Euquinine* or *euchinine*, the ethyl carbonate of quinine, has the advantage of being almost tasteless, an important property in the case of children or fanciful patients, and, according to Fletcher, it is as effective as the more familiar salts of quinine. On the other hand, some tasteless preparations, quinine tannate and quinine bicarbonate, are useless, owing to their insolubility in water.

Quinidine has an action upon the benign tertian parasite comparable to that of quinine.

Continuous drenching with quinine is of little use in persistent cases. It may be necessary, even in benign malaria, to give a course of intramuscular injections in order to cut short the fever. It has been found that cases of general paralysis treated thera-

apeutically with inoculated malaria are extraordinarily amenable to quinine treatment.

Quinine given in regular dosage is known as anti-relapse treatment. Opinions differ as to the best course to pursue. It may be said that it is advisable to keep up the quinine for three months, either by the so-called week-end system, 30 gr. on each of two consecutive days, or 10 gr. once a day for six days.

Alarming pernicious symptoms supervening in an otherwise straightforward case of benign malaria are usually due to a co-existing subtertian infection; this is a much more common complication than is generally supposed, and the case must be treated on the lines laid down for the latter type.

Adjuvants to quinine.—In the acute stage of the disease, with a tendency to nausea and vomiting, all food must be withheld, but the patient should be encouraged to drink freely of water, and the absorption of quinine is assisted by drinking a hot decoction of lemon made from fruit and peel. If vomiting is troublesome, sodium bicarbonate (1 dr.) in warm water should be given shortly after the quinine solution, or, if it is very severe, the stomach should be washed out with small doses of tincture of iodine (30 min. to the pint) and counter-irritation applied to the epigastrium. If quinine, in spite of these measures, is still badly tolerated, smaller doses (5 gr.) given six times during the day may be found more advantageous. Diaphoresis is promoted by the following mixture:

Sol. of acetate of ammonia	℥ii
Spt. of nitrous ether	℥xxx
Aq. camph. co.	℥½

If the spleen is tender, the application of a mustard plaster or a fomentation often gives relief. It is generally held that the absorption of quinine is greatly assisted by the administration of arsenic, and indeed in times of scarcity this drug has been administered in the routine treatment of disease. It is usually given in the form of liquor arsenicalis, 5 min. three times daily. The arsenic may be combined with iron in order to combat the anæmia, as in the following prescription:

Acid sol. of arsenic	℥iii
Ferrous sulphate	gr.ii
Dilute hydrochloric acid	℥iii
Aq. ad	℥½

It may be more advantageous, especially during the convalescent stage of the disease, to prescribe iron and arsenic together in pill form, to which strychnine may be added, as in the following:

Iron hypophosphite	gr.ii
Arsenious acid	gr.⅝
Strychnine sulphate	gr.⅓
Saccharin	gr.⅓

Two or three of the pills are given every night.

Another method of prescribing arsenic is in the form of sodium cacodylate (sodium dimethylarsenite) in ½- to 1-gr. doses hypodermically, as a general tonic and as an adjuvant to quinine.

Warburg's tincture.—A very effective medium for giving quinine, and one of high repute in many places, is Warburg's tincture. This contains, besides quinine, a number of drugs, some of them doubtless inert, although others certainly possess valuable therapeutic properties. The dose is $\frac{1}{2}$ oz., and is repeated after two or three hours.

Cinchona febrifuge is a preparation containing the total alkaloids extracted from cinchona bark, made in the Government factories in India and issued in the form of 3-gr. tablets. Owing to its cheapness it is much in use in that country; it is especially useful in benign tertian infections, on account of the high percentage of quinidine it contains. The average composition of the cinchona febrifuge made by the Government of India is as follows:

Quinine	7.4	per cent.
Quinidine	22.83	„ „
Cinchonine	18.58	„ „
Cinchonidine	5.84	„ „
Ash, etc.	45.35	„ „

Thus it contains 54.65 per cent. of crystallizable alkaloids. The Java febrifuge contains 11.5 per cent. of quinine and a smaller percentage, 5 per cent., of quinidine.

According to Knowles, cinchona febrifuge may be combined with alkaline treatment as follows:

Cinchona febrifuge	gr. 10
Pulv. acidi citrici	gr. 20
Magnesium sulphate	gr. 20
Spirit. anisi	℥ 10
Syrup. simplicis }	āā 3 $\frac{1}{2}$
Aquam	

The dose is 1 oz. three times daily, two-and-a-half-hours after food for one week, then 1 oz. twice daily at the same period after food for a period of two weeks. In order to check vomiting, a dose of 15 min. of 1:1,000 adrenalin in water, or $\frac{1}{2}$ min. of tincture of iodine in water, may be given before the cinchona febrifuge, or if necessary a dose of tincture of opium.

Proprietary drugs.—Esanofele (in pill form) or Esanofelina (in solution) is a drug which has been much utilized in Italy; it comprises both arsenic and quinine. Each pill contains:

Quinine bisulphate	grm. 0.09 (gr. $\frac{1}{8}$)
Arsenious acid	grm. 0.0009 (gr. $\frac{1}{110}$)
Citrate of iron	grm. 0.027 (gr. $\frac{1}{35}$)
Powdered herbs	grm. 0.145 (gr. $2\frac{1}{4}$)

This is virtually what is known as Baccelli's mixture. The dose for a child under 6 years is two pills a day; from 7–14, four; for an

adult, six ; as a preventive it is recommended that two pills be taken every day. This preparation is sometimes recommended on the ground that it contains no quinine, but this is obviously a fallacy.

Mode of action of quinine.—In what way quinine acts has not been satisfactorily explained. Some, reasoning from the toxic influence this drug exerts on many kinds of free amœbæ, say that it acts as a direct poison to the parasite ; they point to the degenerative changes, as evidenced by imperfect staining reaction, exhibited by such parasites as persist in the blood after administration of quinine has been commenced, but this seems to be negated by the observation that malaria parasites may be immersed in quinine solution (1 : 5,000) for some hours and subsequently on injection may produce an attack of malaria. Others maintain that it acts in stimulating the phagocytes, the natural enemies of the parasite. Some experimentalists allege, on the other hand, that it paralyses the white corpuscles. That quinine does not kill all blood protozoa is certain, for it has no effect on the hæmoprotozoa of birds and reptiles, or on the trypanosomes. What is certain is that in man, with the exception of the crescent form of the subtertian parasite, it usually causes the parasite to disappear quickly from the general circulation, for the asexual forms of the benign and subtertian parasites will disappear from the circulation within four days, while crescents will take three weeks or more in a subject who is taking 30 gr. of quinine a day. Another point requiring explanation is that quinine is more effective if withheld till the patient has passed through several attacks of fever ; and that so-called quinine-resistant fevers are usually produced by chronic quinine intoxication.

Plasmoquine (or plasmochin) in malaria.—Plasmoquine¹ (alkyl-amino-6-methoxy-quinoline, formerly known as beprochin) is a compound produced by Hörlein in an attempt to synthesize quinine. The experimental work and the estimation of the therapeutic dosage in man has been carried out by Roehl on canaries infected with *Proteosoma* (*Plasmodium relictum*), when it was found that very small quantities of the drug, when injected into the alimentary canal, would banish the parasites from the circulation of these birds. When given in a dosage of 0·08 grm. daily for five consecutive days, it has a remarkable specific action on the benign tertian and the quartan parasites, which disappear from the blood with a rapidity equal to that seen in the case of quinine ; on the subtertian parasite the effect is not so satisfactory ; but in all three infections, as pointed out by Mühlens, the gametocytes are destroyed

¹ Bayer & Co.

long before the schizonts, so that the crescents of the subtertian parasite (which may persist for weeks in the circulation in quinine therapy) can no longer be found after four days' full dosage with plasmoquine. The spleen is also reduced in size with marked rapidity. Unfortunately, especially in heavy subtertian infections, a cyanosis, probably due to the conversion of hæmoglobin into methæmoglobin is sometimes noted, and, in a few instances, has been followed by methæmoglobinuria. The toxic effects of plasmoquine appear to be effectually counteracted by combining it with minute quantities of quinine. The combination is now (1928) known as plasmoquine-compound and is sold in tablet form, each containing 0.01 grm. of plasmoquine and 0.125 grm. of quinine, which is twice the size of the tablet formerly manufactured. Plasmoquine-compound is comparatively tasteless.

As far as has been at present ascertained, plasmoquine-compound is as effective in treating benign tertian malaria and in preventing relapses as is quinine. In the subtertian form the schizonts do not disappear from the blood with such rapidity as with quinine, but the same specific action on the gametocytes is seen. Crescents disappear from the circulation after three days' full dosage.¹ This compound appears to be well tolerated by children. The following course of treatment with plasmoquine-compound is recommended in all three forms of malaria. The exact amounts are stated of the new preparation of plasmoquine-compound in order to avoid confusion :

For an adult:

(1)	7 days.	2 tablets plasmoquine-compound 3 times daily.
(2)	4 " interval	
	7 " "	2 " " " 3 " "
(3)	4 " interval	
	7 " "	2 " " " 3 " "
(4)	4 " interval	
	7 " "	2 " " " 3 " "
(5)	4 " interval	
	7 " "	1 tablet " " 3 " "

Plasmoquine-compound tablets as formerly manufactured contained each 0.005 grm. plasmoquine and 0.0625 grm. quinine. The maximum daily dose was 12 tablets.)

For Infants: 1 tablet plasmoquine-compound should be given daily.

[i.e. 0.01 grm. ($\frac{1}{8}$ gr.) plasmoquine + 0.125 grm. quinine].

Children between 4 and 5 years: 1 tablet plasmoquine-compound 3 times daily.

Children between 5 and 10 years: 1 tablet plasmoquine-compound 4 times daily.

¹ The Editor has shown that subtertian crescents disintegrate and disappear from the circulation after 0.08 grm. ($1\frac{1}{2}$ gr.) plasmoquine and 1 grm. quinine. With pure quinine treatment, crescents may remain visible in the blood-stream for twenty-eight days and after 56 grm. of quinine.

The course of pure plasmoquine is similar to the above and, when the drug is put up in tablets of 0.02 grm. each, one tablet should be taken three times daily (1 gr.).

Recent observations by the editor tend to show that the tendency to development of toxic symptoms is eliminated by the exhibition of glucose, 1 fl. oz., daily, together with plasmoquine.

The prophylactic action of plasmoquine in the prevention of malaria is now being investigated. Fischer on the West Coast of Africa gave it in doses of 0.05 grm. daily for three consecutive days weekly during a voyage of six weeks' duration. No untoward sequelæ were observed and the drug was apparently successful in preventing malaria infection. Probably if combined with small amounts of quinine it may prove more effective. It is now recommended that for efficient prophylaxis 12 tablets of plasmoquine-compound should be taken weekly.

Salvarsan and its derivatives.—These drugs appear to have some influence upon *P. vivax* (benign tertian), but they seem to have no effect upon the subtertian or the quartan parasite. When given in therapeutic doses in the apyretic periods they do not seem to prevent ordinary relapses. Many practitioners, however, are in the habit of employing weekly injections of salvarsan as an adjuvant to quinine treatment, and there is little doubt that in some cases it acts as a general tonic and improves the physical condition of the patient; but it is in those cases—unfortunately not exceptional—in which syphilis as well as malaria is present that their action is most marked.

Stovarsol (see p. 417) in 4-gr. tablets, dosage one to two tablets daily for ten days, has been claimed to have a curative effect in malaria. It is doubtful, however, whether this is the case, though the drug possesses a marked tonic and stimulating action. Such large doses, 15 gr. daily, as advocated by French writers, are certainly to be avoided, as toxic erythema and other disagreeable sequelæ are liable to ensue. According to some authorities, quinine and stovarsol act better in combination than when given singly.

Treatment of subtertian malaria.—Mild cases of malaria of the subtertian type, due to *P. falciparum*, may be treated on the same lines as the benign forms; and when the quinine per os is retained, and no alarming symptoms supervene, it is advisable to persist on these lines, rather than have recourse to the methods about to be described.

Rest is a most important factor. It is undoubtedly true that the malignancy of many cases of subtertian malaria observed in military service is due, to a great extent, to the exigencies of war.

The sooner after infection a case of subtertian malaria is treated by quinine, the more rapid the recovery and the less likelihood of relapse or of the development of pernicious symptoms.

In the endemic area of blackwater fever, and in persons who have left that area, large doses of quinine do sometimes undoubtedly determine an explosion of that dangerous disease, especially in the cachectic.

Injection of quinine.—The *intramuscular* method is sometimes a painful one, and may be attended with some risk; but, in the circumstances, such possibilities count for little. As indications for intramuscular injection, the inefficiency of oral quinine, its non-absorption owing to severe vomiting or gastritis, the presence of severe, toxic, or pernicious symptoms, or of large numbers of parasites in the peripheral blood, may be taken as guides.

The most suitable readily procurable salt for injection is the hydrochloride or, better, the bihydrochloride (*see* Table below), which is soluble in less than its own weight of water.

SOLUBILITY AND EQUIVALENT VALUE OF SALTS OF QUININE

Those marked with an asterisk are suitable for hypodermic injection

Name of salt	Proportion of the alkaloid in the salt	Solubility in cold water	Amount equivalent in value to one of quinine sulphate
Sulphate	73.5 %	In 800 parts	1.00
Hydrochloride	81.8 %	„ 40 „	.90
*Bihydrochloride	72.0 %	„ 1 „	1.02
Hydrobromide	76.6 %	„ 45 „	.96
*Bihydrobromide	60.0 %	„ 7 „	1.23
Bisulphate	59.1 %	„ 11 „	1.24
Phosphate	76.2 %	„ 420 „	.96
Valerianate	73.0 %	„ 110 „	1.01
*Lactate	78.2 %	„ 10 „	.94
Salicylate	70.1 %	„ 225 „	1.05
*Hydrochloro-sulphate ...	74.3 %	„ 2 „	.99
Arsenate	69.4 %	Slightly soluble	1.06
Tannate	20.0 %	„ „	3.67
*Bihydrochl. of q. and urea	59.2 %	In 1 part	.60

In giving an intramuscular injection, a stout, preferably platinum-iridium needle, should be driven well home, deep into the gluteal muscles, the skin having been carefully cleansed. The solution must be freshly prepared and boiled, and the syringe and needle thoroughly sterilized. A syringe having a well-fitting glass piston and a plugging needle is the best instrument for giving these injections.

The bihydrochloride of quinine may be obtained in 5-gr. tabloids, specially prepared for intramuscular injection. Ampoules containing 9 gr. of quinine bihydrochloride to the c.c. of saline are

on the market. One of these injections may be given into the buttocks daily for three consecutive days at the maximum.

When large numbers of intramuscular injections have to be given the quinine solution may be put up in vaccine bottles fitted with a sterilized rubber cap in a solution of 9 gr. of quinine hydrochloride in 1 c.c. of 0.75-per-cent. saline. The cap is disinfected and the needle of the syringe plunged through it into the bottle.

The best site for an intramuscular quinine injection is the gluteus maximus muscle at a point on a horizontal line with the apex of the great trochanter. This point, of course, is well above the exit of the deep-lying great sciatic nerve, which may be injured by plunging the needle in a false direction. After the injection is made the part should be gently massaged so as to diffuse the solution, and the little wound sealed with collodion. *Quinine ought never to be injected into the neighbourhood of large nerves or blood-vessels, or be permitted to impinge upon the bone.*

It has been shown that a concentrated solution of quinine is rapidly absorbed from the tissues, and that its action upon the parasites in the circulation is almost instantaneous. There appears to be no special purpose in further diluting the quinine for the intramuscular route.

From experiments on quinine solutions Martindale has suggested *mannitol quinine* as being the least irritating; the combination is as follows:

Quinine base	gram. 12.0
Boric acid	gram. 8.4
Mannitol	gram. 7.5
Distilled water to	100 c.c.

1 c.c. contains 0.12 gram. (approx. 2 gr.) of quinine base and 0.084 gram. ($1\frac{1}{2}$ gr.) of boric acid.

This injection contains a reasonable therapeutic dose of quinine. In view of the work of Henry and Brown and others, the quinine in this form should be more potent against the malaria parasite.

Precautions.—It may be well to mention—not with the idea of deterring the practitioner from using the drug in this way, but to impress upon him the necessity for sterilizing the patient's skin at the place selected for injection, and keeping instruments and solutions aseptic—that not only abscess, sloughing, and chronic painful indurations have sometimes followed the intramuscular injection of quinine, but also tetanus. (Fig. 21.)

A localized necrosis of the muscular fibres of the gluteus occurs

after every injection of quinine ; this is followed by œdema and, it may be, a destruction of the blood-vessels, thus rendering the muscle a suitable culture-ground for the tetanus or other organisms which may, as we now know, gain entrance through the blood-stream. The main point to remember is that this method has its *uses* as well as its *abuses*. There is no advantage in repeating the injection day after day in approximately the same spot ; if this is per-



Fig. 21.—Quinine abscess of buttock, developing ten weeks after last quinine injection. (*Orig.*)

sisted in, the most extensive necrosis and hæmorrhage may result. In addition to tetanus and abscess-formation, gas gangrene and general streptococcal septicæmia have been observed. Injection into or near the great sciatic nerve has resulted in paralysis of one leg.

Our personal opinion is that these intramuscular injections of quinine in the dosage advocated are quite sufficient to tide over the pernicious symptoms of malignant malaria and to save the patient's

life. Continued pyrexia does not necessarily indicate that parasites are still active in the tissues.

Subcutaneous quinine as a routine measure had been largely abandoned, owing to risk of superficial necrosis, but during the Great War it was practised by the French in Macedonia and by ourselves in East Africa, apparently with good results. The dosage is 6 gr. to 1 c.c. of saline; either the hydrochloride or bihydrochloride may be used. The injection is given into the flanks, and is followed by massage with carbolic oil.

Quinine by enema.—Quinine may be administered per rectum, and it is especially indicated in babies or very young children, the appropriate dose of quinine hydrochloride being dissolved in water and mixed with an ounce of starch, with a few drops of tincture of opium, and injected as high into the rectum as possible through the nozzle of a glycerin syringe. The dose for adults is usually 30 gr. in 4 oz. of the menstruum. Although the therapeutic effects are said to be good, Fletcher has recently questioned whether any of the quinine is absorbed by this method.

Intravenous injection of quinine.—In pernicious cases, in which it is of importance to obtain a rapid and powerful action of the drug, the injection must be intravenous. The bihydrochloride salt should be used in a dosage of 10 gr., dissolved in 10 c.c. of distilled water. In algid or collapsed cases it may be advisable to add saline and glucose 5-per-cent. injection, in amounts of $\frac{1}{2}$ to 1 pint as well, though in comatose cases it does not appear to be of any distinct advantage. The solution should be boiled in a test-tube before use, and drawn up in a sterile syringe and injected into the median basilic vein, rendered prominent by means of a rubber band. On its introduction into the vein the plunger of the syringe should be slightly withdrawn to observe the entrance of blood into the barrel. The injection should then be made slowly, and at least three minutes spent over the operation. One dose of 10 gr. is usually sufficient to stop the fever, and cause the disappearance of most of the parasites within eighteen hours. The amount of toxin liberated by the rapid destruction of the parasites after intravenous injection may be sufficient completely to paralyse the cardiac mechanism, and death may rapidly ensue. It is much more advisable in cases where the myocardium is involved, to give a preliminary intramuscular injection of quinine, and to follow it up six or eight hours later by a small intravenous injection (6 gr.). It is possible that more frequently repeated 3-gr. intravenous doses are more efficacious than are larger ones given at longer intervals. If great destruction of red blood-corpuscles has taken place, blood transfusion of 300-500 c.c. is strongly indicated.

Treatment of cerebral malaria.—In a threatened cerebral attack ice-bags should be applied to the head at the same time as hot applications to the feet and legs; inhalations of oxygen are advisable; artificial feeding may be necessary. In order to obviate the accumulation of parasites in the brain it has been recommended that the patient should be made to inhale a few drops of amyl nitrite in order to make the parasites more accessible to quinine; and in order to bring the quinine solution into intimate contact with the parasites, adrenalin solution 1:1000—5 min., may be injected intravenously.

In the case of coma or convulsions, one should also take into account the fact that a considerable œdema of the brain and increase of cerebro-spinal fluid have been demonstrated in fatal cases in which no sporulating parasites could be found in the cerebral capillaries. In comatose cases which do not clear up after intravenous injection of quinine (15 gr.), lumbar puncture and withdrawal of 20 c.c. or so of cerebro-spinal fluid may give great relief. Cordes has actually recommended, and performed, puncture of the cisterna magna at the base of the brain, 50–60 c.c. of fluid being allowed to escape. The effect of decompression is striking and immediate. As a general rule, increasing coma after intravenous quinine, especially if accompanied by signs of cerebral irritation, is due to multiple punctate intracerebral hæmorrhages.

Treatment of bilious remittent.—In bilious remittent and other severe forms of malarial fever one must not wait for the remission before giving quinine. To wait for remission or sweating used to be the practice; it was said that to give quinine at any other time was wrong, and that something terrible would happen if the superstition were ignored. *In all grave fevers a full dose, 10 or 20 gr., should be administered at once.* The parasite cannot be attacked too soon. It is desirable to have the bowels freely opened with salts; quinine undoubtedly acts better then.

For vomiting and other severe symptoms, fragments of ice may be sucked, small doses of morphia injected, or counter-irritation applied to the epigastrium.

Treatment of hyperpyrexia.—Hyperpyrexia must be promptly met by prolonged immersion in the cold bath, rectal injections of iced water, ice-bags to the head, etc. At the same time quinine must be injected. Prompt action in these cases is of the first importance, and may save life. If temperature be kept down for three or four hours the quinine gets time to act on the parasites crowding the intracranial vessels; but if temperature be allowed to mount and to remain high the patient is destroyed before the

specific has a chance. The cold bath, therefore, is absolutely necessary. In such circumstances, antipyrin and similar antipyretics are worse than useless. Good rules are to prepare to give the cold bath or cold pack if the axillary temperature reaches 106° F., and to remove from the bath when the rectal temperature has fallen to 102° F.

Treatment of splenic tumour and malarial cachexia.—The enlarged spleen of malarial cachexia is best treated by counter-irritation (linimentum iodi, or ung. hydrarg. biniodid.) and saline aperients combined with quinine, arsenic, and iron. The subjects of hepatic enlargement and abdominal congestion arising from malarial disease of long standing generally derive much benefit from a course of Harrogate, Kissingen, Carlsbad, or other aperient mineral water. When none of these waters can be obtained, a morning aperient saline, kept up for two or three weeks, is an efficient substitute. Aperient courses should, as a rule, be combined with moderate doses of quinine, and be followed by courses of iron and arsenic.

If quinine is being taken when the patient leaves for Europe, its use, in the accustomed dose, should be systematically continued during the voyage and for several months (at least three) after arrival. One finds that malarial cachectics are often allowed to start on the voyage to Europe inadequately instructed on these important points.

General management of a case of malaria.—Every case of malaria with fever should be nursed in bed and treated seriously, for severe symptoms may develop at any moment. It is especially important that the patient should not be left alone in a room, particularly in subtertian infections, as he may become maniacal and may take his life.

Special attention should be paid to the patient's clothing; his feet must be kept warm with bed-socks, and during the stage of perspiration the bedclothes should be frequently changed. Attention to the food is also necessary. During the acute stages it is best to give plenty of water and lemonade to drink, while the food itself should be fluid and easily digestible. During the convalescent stages, if the patient has an appetite, full diet should be substituted, and there is no point in denying to patients who are used to it a strictly moderate amount of alcohol; beer and stout in moderation are useful.

TREATMENT OF BLACKWATER FEVER

Having regard to the frequency with which hæmoglobinuria concurs with malarial infection, and the well-established fact that

quinine may precipitate or determine a hæmoglobinuric attack, the question of the administration of that drug in blackwater fever becomes important.

There can be no doubt that in large doses quinine exercises a certain amount of destructive action on the blood-corpuscles, rendering their hæmoglobin unstable. When, therefore, its toxic influence is superadded to that of the specific cause of the hæmoglobinuric fever, it may be that it supplies the little that is required to determine an extensive liberation of hæmoglobin which, had the quinine been withheld, might not have taken place.

Recommendations.—Patients who are suffering from or are threatened with hæmoglobinuria, or are in the *pre-blackwater state* (p. 50), or who have had this disease before, on the slightest indication of fever should go to bed at once, keep the skin warm and scrupulously protected from draughts, and take plenty of warm fluid; if parasites are present in the blood, the patient should be desensitized by giving gradually increasing doses of quinine, commencing with 1 gr. twice daily and working up gradually to 5 gr. twice daily, together with a moderate dose of calomel. Patients threatened with blackwater fever should not travel; should it become imperative for any reason to move the patient, a small injection of morphia should be given, or he may be kept under slight chloroform anæsthesia during the worst part of the journey. Some believe that by giving large doses of aperient sulphates (1 oz.) every four hours to patients in this state, and thus by the profuse catharsis relieving the hepatic congestion, the onset of blackwater fever may be averted. Intravenous injections of 5-per-cent. glucose in warm saline, a pint at a time, are indicated.

As both clinical and experimental work go to prove that suppression of urine is much less likely to occur if the urine is alkaline, massive doses of sodium citrate, either alone, or together with sodium bicarbonate, should be given until the urine is alkaline. It may be necessary to give as much as 1 drachm at four-hourly intervals until this is produced. If the symptoms be more severe, intravenous injections of sodium bicarbonate, 150 gr. to 1 pint of distilled water, should be administered without delay (Hanschell). It is not advisable to inject more than one pint at a time on account of the very real danger of œdema of the lungs.

If the urine still tends to be suppressed, *caffeine citrate*, 2 gr., twice in the twenty-four hours, should be given as a bland diuretic. In these circumstances hot fomentations should be applied to the loins, or cupping by Fenwick's glasses should be instituted, plenty of bland diluents administered, and an exclusive milk diet ordered

until the albumin has disappeared from the urine. High rectal lavages with hot water have a marked diuretic effect. Indeed, even in the mildest as well as the gravest cases, the free and frequent administration of fluid is a most important measure, whether the patient is thirsty or not, and should be insisted on from the beginning of the attack. When, owing to persistent vomiting, fluid cannot be retained by the stomach, enemata of warm physiological *salt solution* (much less irritating to the bowel, and thus far more likely to be retained than plain water) should be administered repeatedly, 6-8 oz. every half-hour or hour. Turpentine suppositories, mustard plasters and hot fomentations to the epigastrium are useful in controlling or ameliorating the vomiting. If these are not effectual, the salt solution (a teaspoonful to the pint of water), sterilized, may be slowly introduced into the subcutaneous connective tissue of the flank or elsewhere by means of a hollow needle attached by a rubber tube to some improvised reservoir placed one or two feet above the level of the patient. The water is rapidly absorbed, and cannot fail to be useful in washing out the hæmoglobin infarcts which plug the renal tubules and bring about, or at all events contribute to, suppression of urine. In cases with convulsions or coma, 5-per-cent. *glucose solution* given intravenously to the extent of two or three pints is advocated. Marked restlessness may require minute doses of *morphia* ($\frac{1}{10}$ gr.); but the drug, of great use at times, must be employed with caution. This is the only rational and safe systematic treatment of hæmoglobinuric fever. For the very severe anæmia which results, *liquor arsenicalis* (2 min.) may be administered four-hourly. Antipyretic drugs, as antipyrin and phenacetin, are dangerous.

Transfusion of blood has been successfully practised in the high degrees of anæmia which result in some cases after the hæmoglobinuria has ceased. It is necessary to give as much as 500 c.c. if possible, which may be repeated as often as is necessary; the real benefit of this measure results, not so much from the replacement of the blood-corpuscles that have been destroyed as from stimulation of the blood-forming elements, notably the bone-marrow (see p. 668).

Oxygen inhalations are indicated, but are rarely available.

In desperate cases of suppression of urine, Stannus suggests, and has practised with temporary success in one case, incision of the capsule of the kidney.

Nursing is a most important element in the management of blackwater fever. If the stomach will retain food, this should be given in a bland and fluid form, but there should be no attempt to

force feeding, especially with rich and indigestible viands. One precaution against syncope must be sedulously enforced: the patient must not be allowed to sit up, much less to get out of bed, until food has been retained and assimilated, and the risk of sudden death has passed. The foot of the bed should be raised on blocks.

If possible, the subject of a hæmoglobinuric attack should quit the endemic area, and never return to it, or to any malarial locality; a severe attack, or a second attack, implying as it would special liability, should be regarded as imperative indications to this effect.

PROPHYLAXIS OF MALARIA

The basis of malaria prophylaxis is the fact that particular species of mosquitoes are necessary for the propagation of the parasites. Complete extermination of mosquitoes, or even of all anophelines, by antilarval measures has been found to be impossible. It is much more practical to concentrate on particular species which are known to be efficient carriers of the disease. Since many kinds have a particular habitat, special measures are necessary in special circumstances. Beneficial results can be obtained by destruction of the adult insects in dwelling-houses, but it has recently been realized that the range of flight of the anophelines is much greater than was formerly believed.

Drainage, cultivation, and flooding.—Experience has shown that much can be done to free a locality of malaria. Drainage and cultivation where the land will repay the expenditure, permanent and complete flooding where it will not, and where such flooding is possible, proper paving and draining of unhealthy towns and the filling-in of stagnant, swampy pools—these are the more important things to be striven for in attempting the permanent sanitation of malarious districts. In England, Holland, France, Algeria, America, and many other places, enormous tracts of country which formerly were useless and pestilential have been rendered healthy and productive by such means.

In carrying out extensive public works, care should be exercised to provide good subsoil drainage in connexion with irrigation, to provide efficient drainage to carry off superfluous water *before* introducing a larger water supply into a town previously inadequately watered, and to avoid interfering with the natural drainage of a district in constructing railways and so forth. To do anything that may raise the level of the subsoil water in potentially malarial districts is most dangerous.

Anti-mosquito measures.—In order that anti-mosquito

measures may be effectively carried out, it is necessary that a preliminary survey should be made of the malarious district in order to formulate a plan of the anopheline breeding-places. A study of such a survey plan enables the sanitarian to decide definitely upon the localities from which the malaria arises.

In order to prevent mosquito breeding in *streams* and *waterways*, it is necessary to get as even and swift a flow as possible without eddies or backwaters. The stream should be canalized, that is to say, the sides should be sloped at an angle of 45 degrees. Embankments should be lined with large stones and the vegetation cleared from the edges. An occurrence specially to be guarded against during the monsoon is the formation of pools after the subsidence of extra high flood. A stream thus treated is practically self-sterilizing except when we are dealing with a species of anopheline like *A. maculatus* which is specially adapted for life in rocky streams. Springs of water amongst rocks also afford suitable breeding-places to the last named species. Whenever possible canalization should be supplemented by oiling. Subsoil drainage can be employed in place of canalization and, indeed, forms an important feature of estate sanitation in the Federated Malay States.

Seepage, or infiltration of water through bunds or dykes at the bottom of a hill foot, usually forms a fruitful breeding-ground for anophelines. These seepages are especially met with in "paddy" or rice fields. *Running swamps* in the course of a stream in level country form dangerous breeding-spots. They can be dealt with if the vegetation is first removed, when oiling becomes possible. *Borrow pits*, formed usually in the process of railway construction, may, when several years old, form suitable breeding-places. When recently excavated the water is too muddy for anopheline larvæ to thrive, and when the borrow pits contain larvivorous fish they are usually innocuous and in this contingency should not be treated with cresol. *Tanks*, in India and Ceylon, are seldom dangerous, but if the margins are much overgrown with vegetation, certain anophelines may obtain a foothold. When these tanks are used for washing clothes (dhobyng), the soap and other chemical substances employed are fatal to mosquito larvæ.

Rice fields are dangerous when the water is kept in continuous motion through the fields; uncultivated plots in terraced fields that are allowed to become flooded are especially so. In Java the drying-off of the fields throughout a tract on one day each week has been made obligatory and is efficacious without apparently damaging the growth of the rice. To the inexperienced eye there might seem enormous potentialities for breeding anophelines in paddy fields,

but the rice fields themselves are not always to blame, but rather the irrigation ditches. *Standing swamps* are not dangerous when they contain a large population of predaceous insects and fish which prevent much anopheline breeding. In America these undrainable swamps have been rendered less dangerous by dusting with Paris green from an aeroplane.

Mangrove swamps, especially in the Andaman Islands, are associated with virulent malaria due to the breeding of certain species of anophelines, especially *A. ludlowi*, in saline water. Sunlight is necessary for the development of these larvæ, so that the dense virgin mangrove forest is healthy so long as it is daily traversed by tides; but when trees are cut down, or when bunds are constructed to interfere with tidal movements, derelict pools are formed and are gradually diluted by rainfall to a salinity suitable for the breeding of anophelines. Drainage is difficult at sea-level unless there is a big tidal range. In Malaya, owing to the sixteen-foot drop in the tides, it has become possible to install automatic sluice-gates to the bunds.

Smaller collections of water which, if overlooked, may constitute a grave danger by breeding the dangerous species of anophelines, will next be considered. A sagging gutter may hold enough water to support large numbers of larvæ; moreover, a good deal of atmospheric moisture is condensed upon the roofs of tropical bungalows so that the gutters are constantly being replenished even in the absence of rain. It is probably better to remove eave gutters entirely and allow the water to drip into shallow cement drains placed suitably round the bungalow. Holes in rotten trees may breed a limited number of anophelines. One European species, *A. plumbeus*, breeds exclusively in this situation. *Wells* are a certain source of trouble where they are built within native houses and where, in the absence of light, species of anophelines have adapted themselves. In Jerusalem, Palestine and Macedonia generally, they have been found to be the main breeding-place of *A. bifurcatus*, one of the chief vectors of malaria in these regions. In Bombay City the house wells are inhabited by *A. stephensi*.

Anti-mosquito rules generally adopted are:

Surface drains.—These should be as narrow as possible in proportion to the amount of water they have to carry. The sides of the drain should be sloped at an angle of 60 degrees; less steeply in friable soils; grass growing at the bottom of the drain should be pulled out by hand. Lateral drains into the same channel should be alternated so as not to bring in one from each side at the same spot. In some places, as in Trinidad, it has

been found more effective to blast tracks of drains by means of dynamite.

Subsoil drains consist of unglazed collarless pipes buried beneath the floor of the drain sufficient to carry the normal flow from springs and seepages. Unless these pipes are actually functioning for several months of the year, the cost of their installation is not justifiable. They are especially adaptable to ravines, as in the plantations in the Federated Malay States. There it is found advantageous if they are overgrown by a grass covering which prevents silting and overflowing.

Oil.—Crude liquid petroleum is preferable to kerosene oil. Its spreading power can be improved by the addition of 1-2½ per cent. of castor, or coconut oil. The oil may be applied to the water in several ways. Spraying consists of forcing the oil under pressure through an atomizing nozzle from a special machine. Of the various patterns the “Kent” sprayer best suits the capacities of the tropical labourer. Sprayers should be fitted with leather or flexible metal adjustments, as petroleum oil perishes rubber in a few days. For road-side ditches oil carts may be used, but for all purposes the knapsack sprayer is the most adaptable. The best oil for the purpose is a heavy oil which will issue from the sprayer as a fine cloud and spread uniformly over the water. Oil swabs, or cotton-wool steeped in oil and weighted down by a stone, when thrown into water are ideal for rock springs and running streams. In certain malarial districts in the United States oil-soaked sawdust has been found to give a more complete and permanent oiled surface. The material has the advantage of being easily transported. The oil gradually exudes and spreads as an even film over the surface of the water, entering the spiracles and breathing-tubes of the larvæ and suffocating them. In Panama drip cans and barrels are used from which the oil constantly drips from cork wicks or through holes from which nails project. Their value as an oiling agent is less than when sprays are used. Oil must be applied at *seven-day intervals*; any deviation from this rule will afford a generation of anopheline larvæ ample opportunity to hatch out. If properly treated, the vegetation at the margins of the stream or pond should be burned down for a foot on each side, and water-plants such as *Spirogyra* should disappear.

Cresol is the basis of the many disinfectants on the market, and should be present in any compound in a strength of 15 per cent. Being capable of killing larvæ in a dilution of 1:40,000 within three hours, it forms an excellent larvicide, but it kills off all other forms of life at the same time. Fish killed in this manner are distinctly

poisonous if eaten. Cresol is very useful in ponds and standing water when oil cannot penetrate or is blown away by prevailing winds. In Panama the following preparation is used : 200 lb. of finely-crushed resin are thoroughly mixed with 15 gallons of crude carbolic acid : 30 lb. of caustic soda dissolved in 6 gallons of water are added. This mixture, which is highly poisonous to larvæ in a dilution of 1:10,000, forms an emulsion when added to fresh water. It may also be used as a diluent for heavy oil.

Paris green, an expensive compound, is copper aceto-arsenite, and in quantities used for anti-mosquito work, is said to be harmless to other forms of life ; culicine larvæ are not affected in the same manner as the surface-feeding anophelines. The powder should be intimately mixed with one hundred times its weight of finely-sifted dry road-dust and sown by hand, down wind, over the water at the rate of 170 gr. of Paris green per ten square feet of water surface. In America, dusting machines have been invented for this purpose, and in large marshes the services of aeroplanes have been called into use.

Copper sulphate is especially useful in tanks where water is stored for drinking purposes and where sheets of algæ are sheltering larvæ. Its action is not direct upon the larvæ themselves, but is one of starvation by killing off their food supply.

Stoxal of Messrs. Poulenc is a special preparation of formalin or paraform and is regarded by Roubaud as being most destructive to anopheline larvæ, while at the same time harmless to fish, and in this respect superior to Paris green and other arsenical powders. It is an extremely light powder of great buoyancy, and yet so fine and impalpable that its particles can be ingested by the smallest larvæ. Being so light it can be dispersed over great distances by the wind. One centigramme of the powder suffices to kill all anopheline larvæ over one square metre of surface. The surface of the water must be agitated so that the powder sinks and forms a suspension. For ordinary use it is mingled with fifty times its volume of dry sand and the mixture is then distributed by hand or shovel. On reaching the water the stoxal dissociates from the sand-grain and forms a film fatal to anopheline larvæ.

Oil-burning of marshes.—Waste oil is employed. A mixture of light shale and heavy fuel oil has been found best. The marsh is well oiled and the oil then ignited by means of oil-soaked waste. Once the fire has started, and is spreading, it is fed by sprays of light oil ejected from garden syringes. When the heavy oil catches fire, it burns for hours over vegetation and shallow stretches of water. Great numbers of adult mosquitoes can thus be destroyed, shallow

larvæ-containing pools dried up, and even in the case of deeper water-stretches, the larval stages are to some extent eliminated.

The Hay flame-gun or flame projector, manufactured by Messrs. Hubbard Bros. Ltd., Basingstoke, Hants, weighs between 50 and 60 lb. and is a cylindrical steel container filled with a mixture of inflammable oil. The machine will project a continuous jet of liquid fire to a distance of 80-90 ft., lasting for half-a-minute.

The prevention of mosquito breeding in uncovered and unscreened wells has peculiar difficulties. Oiling water with petroleum is apt to mar its taste. Williamson has recommended the liberation of gases and vapours for this purpose in wells. Para-formal (3 oz. per square yard) vapourized at the bottom of a three-foot shaft will kill anopheline larvæ in half-an-hour. Sulphur dioxide acts by acidifying the water. When using gases, wells should be closed, and for this purpose a portable parachute to be lowered into the well has been devised.

Fish as larvicides.—Most top-feeding fish, when placed in a jar, will clear it of mosquito larvæ. At one time it was believed that “millions” (*Girardinus pæciloides*), a small larvivorous fish found in Barbados and Central America, was specially useful in this direction, but further experience has shown that most countries possess fish hardly if at all inferior to the “millions.” In Europe, the goldfish, stickleback and various species of carp are very destructive of mosquito larvæ. In Palestine, Buxton found various species of *Cyprinodon* effective. In Asia and India especially, species of *Haplochilus*, *Ambassis*, *Anabas*, *Barbus*, *Trichogaster* and *Nuria*; in the Philippines, Hawaiian Islands and West Indies, the top-minnow *Gambusia*; in Australia, *Pseudomugil*; and in Africa, species of *Cyprinodon*, *Girardinus* and *Ophiocephalus* are effective. Fish under natural conditions play a limited rôle as controllers of mosquito life.

Plants.—Several species of water-plants have at various times been thought to be inimical or directly poisonous to anopheline larvæ. In Bombay the rootless *Wolvia azziza* forms an impenetrable scum over the water; various kinds of algæ of the genus *Chara* have been thought to be destructive to larvæ by altering the H-ion concentration of the water. In the Philippines dried roots of the genus *Derris*, when dissolved in water, are distinctly toxic to mosquito larvæ.

Killing adult mosquitoes.—The swatting or killing of adult female anophelines in houses has been advocated by the Malaria Commission of the League of Nations as being the most practical method of controlling malaria in those districts in which, for some

reason or other, extensive antilarval measures cannot be carried out. In the case of *A. maculipennis* in southern Europe which permanently installs itself within houses and cattle-sheds, it would certainly appear that this is a practical solution ; but it has been pointed out that this method is by no means so applicable in the tropics on account of the construction of the houses, which permits mosquitoes to enter or leave with ease. After feeding, most species of anophelines rest on the wall or other suitable resting-place relatively close to where they obtained their blood-meal, but those which have digested the meal and are ready for flight, depart from their daytime resting-place soon after dark, or soon after daylight. In screened buildings, those that are ready to depart collect on window screens or doors during these periods and thus may be easily destroyed. Recently engorged anophelines at rest on walls of buildings are relatively easily killed by an ordinary fly-swatter. A room provided with light-coloured walls makes the task much easier. Spraying with 1-per-cent. cresol is efficacious as it stupefies the insects, which can subsequently be destroyed by swatters. The dark corners of buildings and tents should always be searched, as there the insects tend to congregate, especially in cold weather.

The keeping of domestic animals in the vicinity of buildings, especially cattle, horses and mules, attracts anophelines away from human dwellings. This is especially the case with *A. maculipennis*, which finds the blood of these animals more attractive than that of man. It is essential for the success of this plan that the dwelling-houses should be airy, dry and clean, and that the stables should be relatively dark and damp, continuous occupation by animals being necessary.

General consideration of anti-malaria measures.—It has been pointed out by the Malaria Commission of the League of Nations in the Second General Report, that, having regard to the present state of knowledge, the correct anti-malarial practice is an endeavour to reduce the incidence and severity of the disease. Measures designed to accomplish more are not usually a wise proposition and can be justified only in exceptional circumstances, nor is it always necessary to deal with malaria by a method arising directly out of the knowledge that the disease is transmitted by mosquitoes. As a result of inquiries in England and Holland, much of the reduction in incidence and severity of malaria is certainly not due to anti-mosquito measures so much as to general improvement in the condition, welfare and housing of the inhabitants. In any country and in any area there must be preliminary examinations to ascertain the particular methods best suited to

local conditions; any one or two methods should be employed in order that the standard of execution should be high.

The first most important measure is to arrange for the treatment of the disease by quinine. In certain parts of Europe the gratuitous distribution of quinine is the only anti-malarial measure which the countries concerned can afford. A further advance consists in the organization of a definite system for the satisfactory diagnosis and efficient treatment of the disease. The good results of early diagnosis and efficient treatment are more apparent in the reduction of the severity of the disease than in the reduction of its incidence. A primary measure of importance is the destruction of infected anophelines in houses.

Of all indirect measures of reducing malaria the greatest importance is attached to schemes of *bonification* which aim at the improvement of the economic and social condition of the people, their general well-being and standard of life. In Italy, more especially, this plan has been followed out. The inhabitants there do not regard bonification as an anti-malarial measure; in fact in some instances it may increase the abundance of anophelines in the areas reclaimed from the drainage of swamps; but they do know that in an area where bonification is complete, the inhabitants settle permanently in better houses and are all in other circumstances of a moderately good standard of life.

Whenever possible, advantage should be taken of the knowledge that anopheles mosquitoes rest in cowsheds, stables and pigsties in which animals are kept, in preference to dwelling-houses. Therefore these buildings should be kept separate from the dwelling-house and when possible should be interposed between the house and the chief mosquito breeding-grounds.

Location of dwelling-houses.—The inhabitants of malarious districts ought to live in villages or towns with well-paved streets and courts, going out to cultivate their fields during the day, but returning to sleep in the town before nightfall. Houses should be placed, if possible, on high and dry situations, a clay soil being avoided. All forest undergrowth should be cleared away. It is unwise in countries such as Africa, where nearly all Europeans suffer from chronic malaria, to place dwelling-houses in exposed situations, or where high winds are apt to produce chills and consequent fever relapses. For the same reason, in elevated situations houses should be well sheltered by trees planted at some distance from the premises, or by higher ground. In the neighbourhood of houses the felting of natural grass should, if possible, be preserved, or, if it be disturbed, replaced immediately, or the exposed soil covered with rammed clay or cement. It is unwise to have flower-beds or vegetable gardens near bedroom windows, or to allow water from bathrooms or cookhouses to flow over the ground in the vicinity of the house, or to keep water unchanged in tubs or water-butts for mosquitoes to breed in. Pools and puddles of stagnant water should be filled

up and turfed. Water-butts and cisterns should be screened, and sagging roof-gutters rectified; discarded tins, jars, pots, bottles, and all rubbish capable of holding water in which mosquitoes could breed should be got rid of, and plants or trees in which collections of water occur should be cut down.

Screened houses with verandas and rooms protected by a mosquito-proof metal screening are made use of in many malarious countries. These houses have the disadvantage of not being so cool and airy as an open bungalow. The material used for screening is called Monel metal and is composed of nickel 67 per cent., copper 28 per cent., and other metals 5 per cent.

Danger from the vicinity of natives.—Seeing that in malarious localities a large proportion of the native children harbour the malaria parasite, and that a large proportion of the anophelines in the neighbourhood of native houses are infected, it is manifest that to visit native quarters when mosquitoes are feeding, especially in the evening or during the night, is fraught with danger. For the same reason the European should build his house or pitch his camp well away—a quarter-of-a-mile at least—from native quarters, and beyond the flight of infected anophelines, nor should native children be allowed to frequent European establishments.

Cultivation of trees and plants.—Much was expected at one time from the cultivation of eucalypti of different species—particularly *Eucalyptus globulus*—as a means of suppressing malaria. Specific virtues were attributed to its balsamic exhalations.

Native experience to be consulted.—It is unwise to build where the natives say the neighbourhood is unhealthy; natives generally know such places. Neither, if it can be avoided, should a stay be made where the natives are anæmic and have enlarged spleens—sure indications of an unhealthy district.

Mosquito-netting.—It is very necessary that the mosquito-netting used should be of reliable quality and should keep out all mosquitoes. In order to do so it should contain as many as 25 or 26 holes to the square inch.¹ (Fig. 22.) The best varieties are known as “bobbin” netting, and should be woven of 30’s cotton; by this is meant that 1 lb. of the thread will reach 30 times round a circumference of 840 yards.

The nets must be used invariably. They should be tucked up underneath the mattress before retiring to bed. Some prefer to allow the net to hang down so as to reach the floor, but if this be done, care should be taken to see that it is in contact with the floor at all points, since otherwise the insects may crawl in underneath. During the daytime the net should be rolled up and placed behind the head of the bed, and all necessary precautions should

¹ It is necessary to explain that the square inch of the net trade is not that of the mathematician; it means that the count is made along two lines of holes which fall within an opening one inch square. (Fig. 23.)

be taken to see that it contains no mosquitoes before being arranged for the night, otherwise it becomes a mosquito "trap" and not a protection. Light



Fig. 22.—Mosquito netting, 25/26 holes to the sq. inch.
(*MacArthur, Jl. R.A.M.C.*)

attracts mosquitoes, therefore the cautious tropical resident will see that he is adequately protected by his mosquito-netting before going to rest in a brightly illuminated room. For the same reason the blinds are best kept down while preparing for the night, to be drawn up again immediately the light is put out.

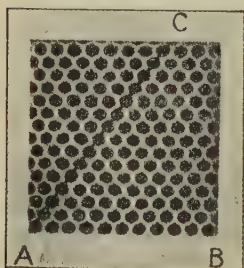


Fig. 23.—Shows the correct method of counting the mesh of cotton netting. The mesh of this net is the sum of the counts made along the lines A B and A C, the hole at A being counted twice.
(*MacArthur, Jl. R.A.M.C.*)

The body should be covered up during sleep, and every precaution (e.g. fires) that circumstances permit should be employed to keep mosquitoes away.

The subjects of malarial infection are dangerous to their companions; they should therefore be avoided, or, if this is impracticable, compelled to sleep under efficient mosquito-nets. It will prove a truly economical procedure to supply natives liberally with quinine; this should go hand-in-hand with other steps that may be taken to render a place salubrious.

Mosquito repellents.—Mosquitoes may be driven out of railway carriages, ships,

or barges by careful fumigation. For this purpose various substances have been recommended, of which pyrethrum powder is probably the most effective. Sulphur dioxide, when used in the Clayton apparatus, and the vapours derived from cresol or hydrocyanic gas are also employed.

For personal use many oils and ointments have been advocated; they are smeared on the hands and face. The proprietary preparation known as Sketofax is recommended by many. Bamber oil has a big reputation; this consists of oil of citronella $1\frac{1}{2}$ parts, kerosene 1 part, coconut oil 2 parts, made up with 1-per-cent. carbolic acid. Cod-liver oil rubbed on hands and face is highly recommended.

The following mixture, has the additional advantage of reducing the irritation of insect bites :

Ol. cinnamomi	3ii
Ol. cajuputi	3i
Formalin (40-per-cent. formaldehyde) .	3i
Alcohol (90-per-cent.) ad	3iv

The irritation of a bite may also be allayed by rubbing the puncture with a moist cake of soap, or by applying 1-per-cent. alcoholic solution of menthol, or a 1 : 20 carbolic solution. Hydrogen peroxide or weak ammonia solution are also useful.

A dilute solution of magnesium sulphate applied to the skin is said to act as a preventative against mosquito-bites; it has the advantage of being cheap and not irritating. The juice of a fresh-cut lime fruit rubbed well into the skin and allowed to dry is an excellent preventative.

These measures are undoubtedly of some value, but they are tedious and sometimes disagreeable to apply, and must only be looked upon as adjuvants to other measures to protect from mosquito-bites.

Mosquito-protected houses.—It has been proved experimentally and practically that complete protection from mosquito-bite, and therefore from malaria, can be secured by having the dwelling-house protected by wire gauze, ordinarily known as "screen-cloth," the mesh not larger than fourteen strands to the inch, in the doors, windows, chimneys, and ventilators.

In order to calculate the mesh, it is necessary to count the number of holes to the inch, since the strands intersect at right angles. The inch is measured along one of the two lines of holes, and from centre to centre of wires.

Imperial Standard Wire Gauze bears a descriptive number indicating the diameter of the wire employed; wire of gauge 30 has a diameter of

0.0124 inch. Of the various metals used in the manufacture of screen-cloth, an alloy called Monel metal is undoubtedly the best, as it does not corrode in a damp climate; but it is expensive, being almost twice as dear as copper.

Some such arrangement as this is now a feature in the domestic architecture of malarial countries, and it is especially necessary in the case of hospitals, where, if the whole building cannot be protected, at least one or more isolated wards should be screened and kept ready for malaria patients, as well as for convalescents from the disease.

Prophylactics.—As regards the use of quinine as a prophylactic, opinions are divided. The experience of the Great War was, on the whole, to discredit its prophylactic value. The practical outcome is that quinine prophylaxis is inapplicable to scattered bodies of men under inadequate medical supervision.

Yorke and Macfie have shown that under experimental conditions the sporozoites injected by an infected mosquito are not destroyed or harmed even when the patients are taking 30 gr. of quinine daily; that is to say, the therapeutic dose of quinine does not prevent the onset of a malarial attack; in other words, against the sporozoite, quinine is apparently ineffective (*see* p. 35). However, that quinine has no direct action upon the plasmodia in whatever stage, appears to have been shown by Mühlens and Kirschbaum who mixed a quantity of malaria blood with a solution of quinine, 1:10,000, leaving the mixture for twelve hours, but yet were able to infect a patient by direct inoculation and, still more, were able to show that *A. maculipennis* may still be infected by feeding on a malaria subject who is taking quinine.

Whatever may be thought of quinine prophylaxis as an army measure, there can be no doubt that most residents in tropical countries lay great store by it, and it is among the European officials and settlers on the Congo and in East Africa that a systematic quinine prophylaxis is most appreciated. It is therefore, for the present, advisable to give 5 gr. of quinine hydrochloride in liquid form, every night, or 15 gr. twice weekly, or on a week-end system for two consecutive days (Koch) towards evening in highly malarious countries.

Tea, coffee, and very small doses of alcohol are also decidedly of service in malaria prophylaxis; but they should be used in strict moderation, the last being taken only after the work of the day is over, and there is no longer any necessity for going out in the sun. Crudeli speaks highly of lemon decoction as a

prophylactic ; its use can do no harm, and it is a pleasant, slightly tonic, and slightly aperient beverage, well suited as a drink in hot climates. The decoction made from one lemon may be taken daily in divided doses. *Plasmoquine* or plasmoquine-compound in tablet form, two at night-time daily, appears to have a definite prophylactic value in malaria, though sufficient time has not yet elapsed since its introduction to test whether it is of permanent value.

Education.—By one, or other, or all of the measures indicated above, much can be done to mitigate or avoid endemic malaria. Perhaps the most important initial measure in the struggle with the pestilence is the education of the inhabitants of malarial countries in the mosquito-malaria theory. Sanitary measures can rarely be carried out effectually without the co-operation of those whom they are intended to benefit ; and this cannot be secured unless the rationale of their operation is understood. Therefore, those responsible for the public health in malarial districts should, by one means or another, indoctrinate the people in the mosquito-malaria theory.

A knowledge of the morphology and habits of the anopheline mosquitoes is absolutely essential in the study of malaria (*see* Appendix, p. 810).

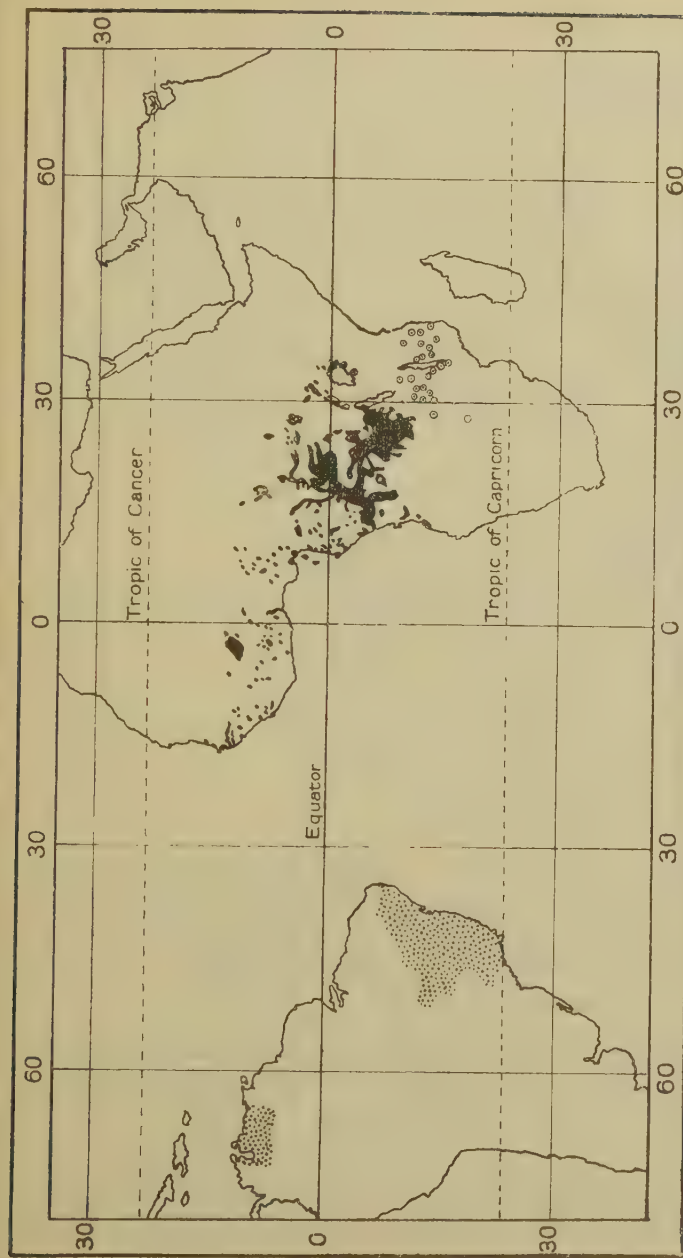
PROPHYLAXIS OF BLACKWATER FEVER

Blackwater fever now being recognized as a complication of malaria, its prophylaxis is essentially the same as that of malaria, but it is necessary to insist that in blackwater-fever districts those who are the subjects of malaria should take quinine systematically, never in an irregular fashion, and should avoid, if possible, undue fatigue and chill.

On leaving the endemic area they should be especially careful to continue the use of quinine in the accustomed doses at the accustomed intervals for at least six months after their arrival in Europe. Most of the cases of blackwater fever seen in Britain are attributable to neglect of this precaution and to a big dose of quinine taken for a relapse of a malarial infection supposed to have died out. Those who have had blackwater fever should gradually habituate themselves to quinine, beginning with minute doses— $\frac{1}{2}$ gr.—slowly increased to 5 gr., which dose they should take daily while under the endemic influences, and for at least six months afterwards.

The scientific prophylaxis of blackwater fever rests upon the early recognition and adequate treatment of all cases of subtertian

malaria, however slight and evanescent their symptoms may appear to be. In other words blackwater fever is an expression of inadequately or incompletely treated subtertian malaria. There is reason to believe that in the combination of plasmoquine and quinine we possess a means of more rapidly extirpating the subtertian parasite than was formerly the case.

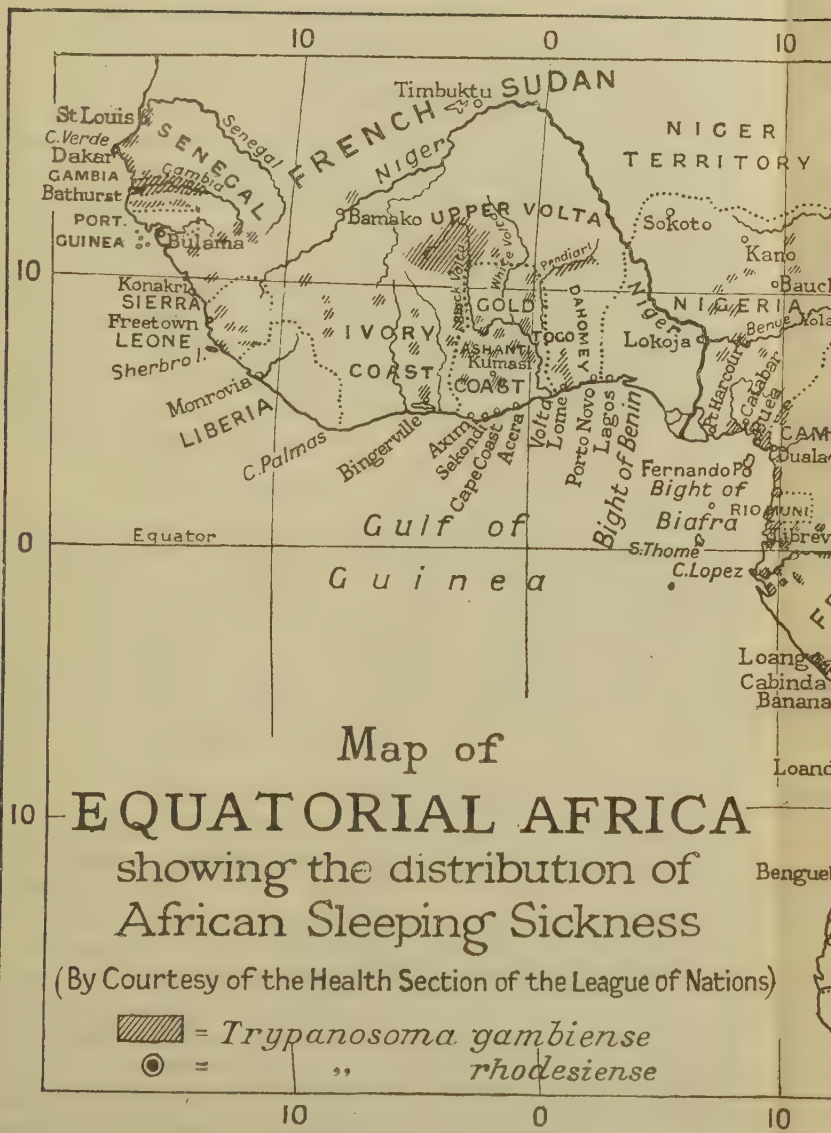


Geographical Distribution of Trypanosomiasis

Cribb & Co

■ = *T. gambiense* ●● = *T. rhodesiense* ●●● = *T. cruzi* in man

MAP I



CHAPTER III

HUMAN TRYPANOSOMIASIS

Definition.—Morbid conditions produced by parasites belonging to the genus *Trypanosoma*, including irregular chronic fever, skin eruptions, local œdema, adenitis, physical and mental lethargy and, in a large proportion of cases, death.

The trypanosomes are blood parasites which are widely distributed in animals, especially in big game, in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. The parasites and the diseases they evoke will be considered separately. The geographical distribution of human trypanosomiasis is shown in Map I; that of the African forms in Map II.

I. AFRICAN HUMAN TRYPANOSOMIASIS

History.—Sleeping sickness has been known for well over a century, but it was not till some twenty-seven years ago that the pathogenic cause was definitely recognized. In 1901 Forde encountered a trypanosome in the blood of a European suffering from fever in Gambia. In 1902 Dutton found a similar organism in the blood of a native of that colony, and suggested the name of *Trypanosoma gambiense* to designate the parasite. In the same year Castellani found the trypanosomes in the cerebro-spinal fluid as well as in the blood of sleeping-sickness cases in Uganda; and his suggestion that the parasite is the cause of the disease was fully confirmed by Bruce, Nabarro, and others (Figs. 24, 25).

GAMBIENSE SLEEPING SICKNESS

Geographical distribution. (Map II.)—The distribution of this disease corresponds roughly with that of the tsetse-fly, *Glossina palpalis*.

Etiology.—Neither age, sex, occupation, nor race *per se* has any influence on the susceptibility to trypanosome infection, except in so far as those factors conduce to opportunity. Thus, occupations (boatmen, fishermen, water-carriers) which imply a frequenting of the waterside haunts of the glossina conduce to infection. In common with other trypanosomes, *T. gambiense* (Fig. 25), as seen in fresh blood, is an active, wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. Dividing forms are sometimes met with.

There is no uniformity in the number of parasites present in the blood: sometimes they are fairly abundant, one or two in

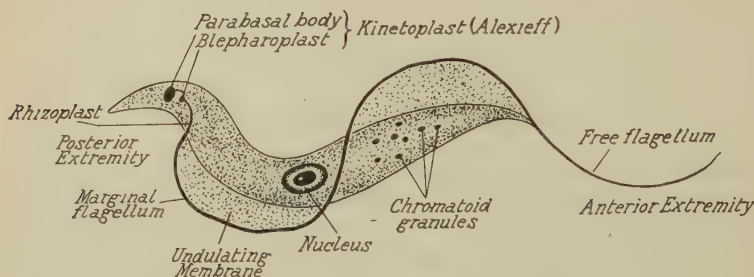


Fig. 24.—Schema of trypanosome. (After Dobell.)

each field of the microscope; at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single specimen; in some instances they tend to recur cyclically at intervals of a week or more. On the whole, although



Fig. 25.—*Trypanosoma gambiense*: various forms from blood and cerebro-spinal fluid.

a, Elongated posterior extremity; *b*, blunt ditto; *c*, *d*, and *e*, dividing forms; *f* and *h*, probably sexual forms; *g*, small round forms from cerebro-spinal fluid.

this is by no means invariably the case, the parasites are most abundant in the blood during the febrile attacks to which the hosts are so subject. The blood appears to be not their only or principal habitat. They are usually found with ease in the enlarged lymphatic glands, and also occur in the cerebro-spinal fluid, as well as in that of the serous cavities. They have been found also in

the substance of the solid organs, including the brain, where they are distributed throughout the tissues outside the blood-vessels.

The parasite may be cultured on N.N.N. medium (*see* p. 861). It can usually be inoculated into most mammals, including all the ordinary domestic and laboratory animals, and is especially pathogenic for the rat, but considerable variations in virulence are encountered. Monkeys, especially *Cercopithecus patas*, and dogs are especially susceptible, while amphibia and reptiles are immune. Inoculation of susceptible animals may be used for demonstrating the presence of the parasite when they occur in very scanty numbers in the peripheral blood, and is sometimes successful in those rare cases where they cannot be found after careful microscopical examination.

As shown by Laveran and others, these trypanosomes undergo agglomeration both in blood and in artificial cultures when exposed to unfavourable biological conditions.

How long a trypanosome infection may persist in the human body has not been definitely determined, but there is direct evidence that it may continue for several years. From what we know of the incubation period of sleeping-sickness, it is not improbable that this period is sometimes greatly exceeded, and may extend to seven years or longer.

Transmission.—This trypanosome is not transmitted hereditarily in human beings, although the organisms have been found in the placental blood of infected rats, as well as in the livers of their embryos.

Rôle of the tsetse-fly as transmitting agent.—There is no evidence that biting flies other than the tsetse are concerned in the spread of human trypanosomiasis, but there are apparently two ways in which this fly is able to transmit the trypanosome: (1) cyclical, (2) mechanical.

(1) *Cyclical transmission.*—*T. gambiense* undergoes an endogenous cycle of development in the circulating blood of the vertebrate. Certain short forms are regarded as the adult or metacyclic type, and they alone are responsible for carrying on the exogenous cycle. When taken up into the gut of the fly (Fig. 26) the trypanosomes first multiply in the mid-gut, and if the contents of the intestine at this stage are injected into the susceptible animal they do not convey the infection. After an elaborate development, lasting 12–20 days, the infective forms of trypanosomes become congregated in the salivary glands. (For further details, *see* p. 683.)

There is no doubt now that transmission ordinarily occurs through the bite of infected flies, the trypanosomes passing through the salivary duct in a similar manner to the sporozoites of the malaria parasite. The adaptation of *T. gambiense* to *G. palpalis* is remarkably specific, for this parasite has so far been found incapable normally of development in any other species of tsetse-fly, though, under certain conditions (according to Kleine, Bruce, and Rodhain), it can develop in *G. morsitans*

(Plate IX), and is then known as *T. rhodesiense*. There is no evidence that the tsetse-fly can transmit the trypanosome to its offspring.

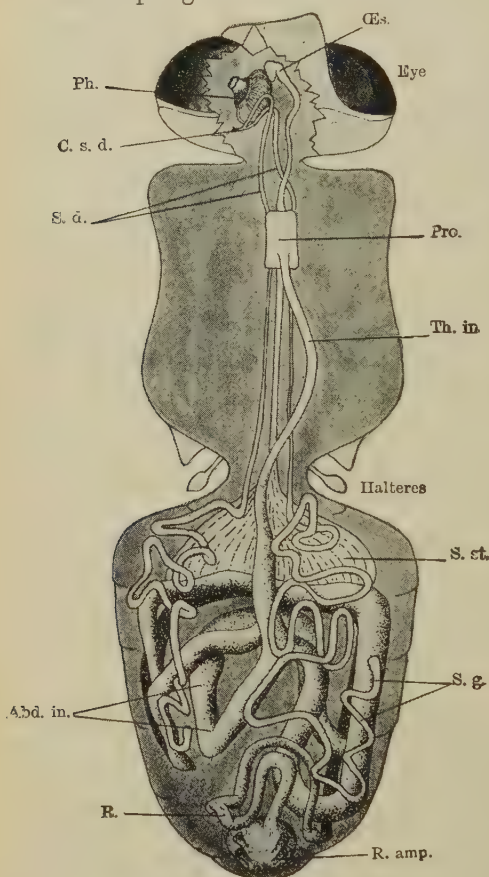


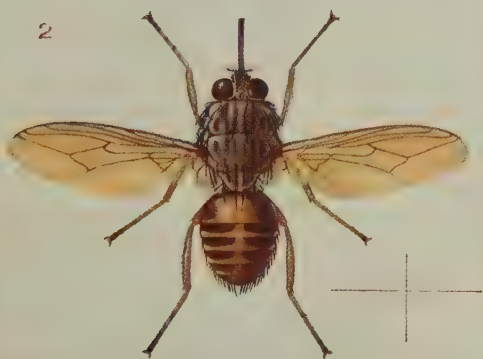
Fig. 26.—General view of digestive tract of *Glossina palpalis*. (After Minchin, "Report on Sleeping Sickness to the Royal Society.")

Ph., pharynx; CEs., oesophagus; C. s. d., common salivary duct; S. d., salivary ducts; Pro., proventriculus; Th. in., thoracic intestine; S. st., sucking stomach; S. g., salivary glands; Abd. in., abdominal intestine; R., rectum; R. amp., rectal ampulla.

(2) *Mechanical transmission*.—Duke, in Uganda, on epidemiological grounds, has suggested that mechanical transmission by the glosina of a virulent strain of *T. gambiense* from man to man may be responsible for epidemics.

Reservoir-hosts.—Formerly it was considered that man acted as the sole reservoir of infection, but recent work has considerably modified this view. It has been proved that eleven common kinds of antelope (bushbuck, reedbuck, and waterbuck) can be inoculated with *T. gambiense* by feeding upon them experimentally-infected tsetse-flies; furthermore, it has been established that certain of the marsh-haunting antelopes, especially the situtunga (*Limnotragus spekei*), are quite commonly infected under natural conditions with an organism thought to be *T. gambiense*. Duke found that antelopes of this species persisted in an infected state in the

islands of Lake Victoria Nyanza four-and-a-half years after the population had been removed by Government orders as an attempt to check the spread of sleeping sickness.



TERZI.

1, *Glossina palpalis*.

2, *G. morsitans*.

TSETSE-FLIES.

PLATE IX

Speke's antelope (*L. spekei*, Fig. 27) is a handsome animal standing 36 in. high at the withers, the buck possessing fine spirally-twisted horns. In ground-colour it is of a uniform greyish-brown, but the head is adorned with white ocular and cheek spots and a white chin. A very wary creature, living in dense and impenetrable papyrus, it is seldom seen or shot by Europeans. The hoofs of this antelope are long and widely splayed, an admirable adaptation to its habitat, but when living on dry land they become shorter and modified accordingly.

The domestic stock must be now considered to constitute a reservoir of infection for man, since *T. gambiense* has been found



Fig. 27.—Situtunga antelope. (Wellcome Bureau Sci. Res.)

by various observers in oxen, goats, and sheep in Tanganyika Territory and East Africa.

Pathology.—The chief lesions are found in the lymphatic glands and in the central nervous system; there is general enlargement, with congestion, and, it may be, hæmorrhage of the lymphatic glands, especially those of the triangles of the neck and submaxillary region and the mesentery.

No gross lesions of the nerve-centres, nor of any other organ, have been described as invariably present; but in every case indications, principally microscopical, of an extensive meningo-encephalitis can be demonstrated. In a proportion of instances congestion of the meninges, effusion of lymph, and increase and turbidity of cerebro-spinal fluid, are found. In all cases, as first pointed

out by Mott, there is an extensive small-cell infiltration of the perivascular lymphatic tissue throughout the brain, cord, and meninges, varying in amount in different cases and in different anatomical regions. The invading cells are glia cells, lymphocytes, and morular cells (Mott); the latter are fuchsinophile hyaline cells, analogous to those found in granulomata (Peruzzi). (Fig. 28.) This, the essential pathological feature of sleeping sickness, recalls the very similar condition in general paralysis of the insane. The lumina of the vessels

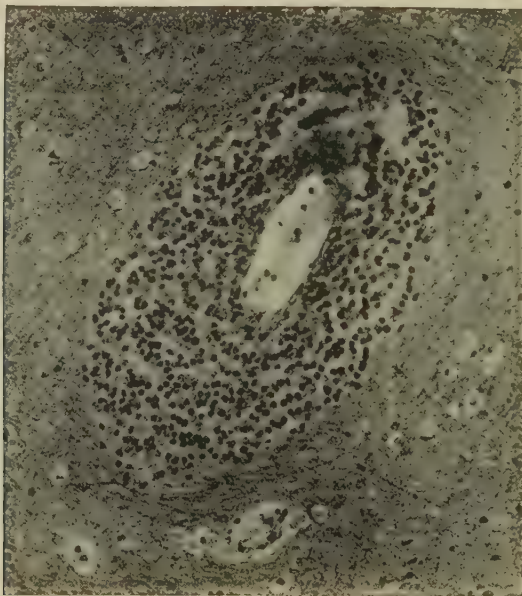


Fig. 28.—Section of brain in sleeping sickness, showing round-cell infiltration filling perivascular space. (Orig. case, Dr. A. C. Stevenson, "*Trans. Roy. Soc. Trop. Med. and Hyg.*")

are contracted, and their walls are thickened. The cells of the spinal cord usually show fewer changes than those of the medulla and the cerebral cortex. Recent experimental work by Yorke, Wolbach, and Stevenson has shown that the lesions of the lymphatic and nervous tissue are due to actual invasion of the solid organs by the trypanosomes, for they have been seen in the brain tissue, mainly in the frontal lobe, pons, and medulla, where they can be demonstrated in masses or nests (Fig. 29), with no definite relation to the blood-vessels. Trypanosomes often occur in the cerebro-spinal fluid, which they enter from the choroidal plexus where, as Peruzzi has

shown, they occur in masses in active stage of division. There is said to be an increase in the lymphatic tissue of the lymph follicles and Peyer's patches of the small intestine. The spleen is usually moderately enlarged, and the trypanosomes have been demonstrated in the pulp tissue.

Peruzzi, in his recent remarkable researches into the pathology of experimental trypanosomiasis in monkeys (League of Nations Report), has shown that myocarditis of a severe degree is frequently present, and that this myocarditis is due to massed collections of trypanosomes in the muscle-cells where many have assumed a

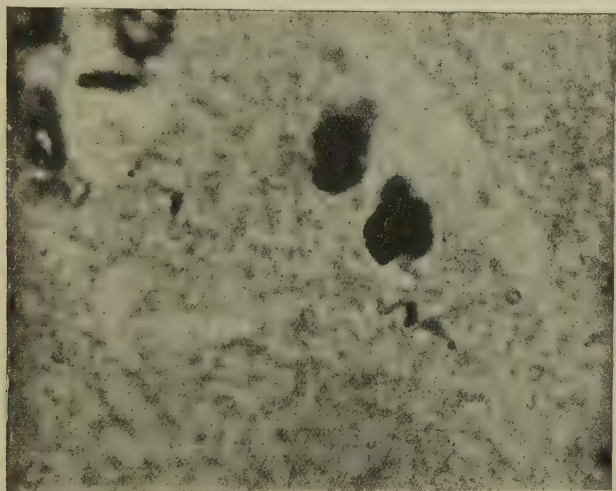


Fig. 29.—Microphoto of frontal lobe of brain in sleeping sickness, showing trypanosomes in grey matter. (Orig. case, Dr. A. C. Stevenson "*Trans Roy. Soc. Trop. Med. and Hyg.*")

leishmanoid phase. This discovery has opened up an entirely novel conception of the true pathology of this form of trypanosomiasis which has some relation to that of Chagas' disease (see p. 127). It explains the intermittent appearance of the trypanosome at irregular intervals in the blood-stream, the cardiac complications frequently observed, and the presence of trypanosomes in the cerebro-spinal fluid when they cannot be found in the blood.

Symptoms.—The *incubation period* of the glossina-conveyed disease and that resulting from direct artificial inoculation seem to be about the same, from two to three weeks, in the case of dogs, horses, and monkeys. As regards man, observations are too few to warrant anything like a definite statement on this

point, but in one or two instances circumstances seem to point to a similar incubation period. The bite of an infected glossina is followed, in a proportion of cases, by a degree of local irritation of greater or less severity. This subsides in the course of a few days, to be followed, sooner or later, by fever, which may last a week or longer, and may be accompanied by the appearance, in Europeans at all events, of a peculiar type of erythema and a certain amount of serous infiltration of the connective tissue. A form of hyperæsthesia, known as "Kerandel's symptom," is usual, though not invariable; if the patient strikes a limb against any hard object, a degree of discomfort amounting to actual pain is experienced, the sensation being slightly delayed. In time the fever subsides more or less completely, to recur at irregular intervals of days or weeks. The fever is sometimes mild, sometimes severe, and occasionally hyperpyrexial (106.6° F.). the evening temperature being always the highest. The fever may last for weeks; the apyretic period may be equally prolonged. On the other hand, the fever may be continuous. Irregularity of degree and duration is a feature of the fever, and also of the other clinical manifestations of trypanosomiasis. In time the patients become debilitated, anæmic, feeble both intellectually and physically. Headache is very often complained of. The heart's action is generally rapid and easily excited. The cervical glands and the glands of other parts of the body enlarge and may become tender. It may be that only one gland is visibly involved, or there may be a recognizable general polyadenitis, including the abdominal glands. The implicated glands may be very prominent, or they may not be easily felt. In the early stage of the infection they are soft, later they are indurated. Sometimes they are painless, sometimes distinctly painful and tender, rarely suppurating. This condition of irregular fever, of debility, of polyadenitis, of slight anæmia, may go on for months, or even, in some instances, for years. (Fig. 30.)

A proportion of cases may terminate at this stage. Considering that the disease may present at various stages periods of quiescence, which in some instances may be very prolonged, it would be rash to say whether in any instance of apparent recovery we are dealing with a radical cure, or merely with one of these long periods of latency. But experiments and observations by Laveran and others in other forms of trypanosome infection, as well as cases of the disease in Europeans, justify the belief that occasionally the parasite does die out spontaneously.

It would appear that in a given area and in a given population

there is a tendency for the virulence of the local trypanosome to decrease with lapse of time. Thus, the trypanosome of Southern Nigeria, where sleeping sickness presumably has long been endemic, is less virulent and much more amenable to treatment than that of Uganda, where it is of recent introduction.



Fig. 30.—Enlargement of cervical lymph-glands in trypanosomiasis.
(*Dr. F. K. Kleine.*)

Remarkable features of human as well as of animal trypanosomiasis are the skin affections and the local œdemas. In many of the lower animals affected with their special trypanosomes, in addition to fever and physical lethargy, papular and pustular eruptions are not uncommon; and in man, especially in negroes, an exceedingly itchy papular eruption is a common symptom.

In the European, and possibly in the negro—but in the latter, in consequence of his colour, not so evident—extensive skin areas are affected with a fugitive, patchy, frequently annular erythema (Fig. 31), usually most evident on the chest and back, but also very often on the face, legs, and elsewhere. This erythema seems to occur most frequently and most distinctly in the earlier stages of the

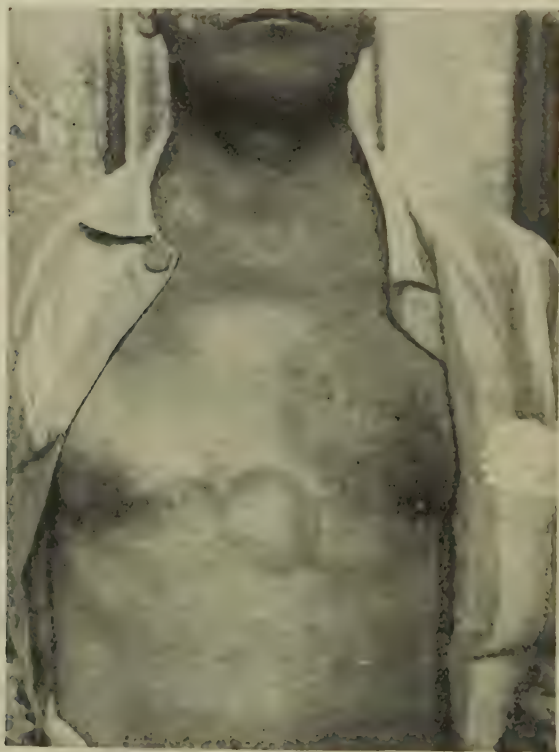


Fig. 31. — Rash of human trypanosomiasis. (Photo: R. McKay.)

infection. Some of the patches may extend to six inches or even a foot in diameter, their margins fading off insensibly into the surrounding normal skin. Sometimes the erythema takes the form of large rings, occasionally complete, more frequently interrupted and irregular. Erythema nodosum sometimes occurs. Pressure or any irritation of the skin gives rise at once to transient congestion from vaso-motor paralysis of the skin capillaries.

In some of the lower animals a usual feature is cedema of certain

parts of the body, especially the sheath of the penis, the under-surface of the abdomen, and the neck. Similar though less extensive œdemas occur in man, in whom they are most apparent in the face and about the site of the erythema. In many instances there is a general fullness of the features which, together with concomitant flushing of the face, is apt to convey a false impression of sound health.

Neuralgic pains, cramps, formication, and paræsthesiæ of different kinds are not uncommon. In two of Manson's European cases, recurring orchitis, accompanied by an increase of parasites in the blood, was a feature. Painful local inflammatory swellings, which after a time subside without suppuration, have been seen in three cases; periostitis of tibiæ once. A toxic irido-cyclitis and choroiditis and deep œdema of the lower eyelid are sometimes met with. The eye symptoms are not so evident in man as in the lower animals; keratitis in infected dogs being comparatively frequent.

In most cases the spleen is enlarged, sometimes enormously so, the swelling fluctuating with the fever. The liver also may be enlarged. As the patients affected with trypanosomiasis are usually the subjects of malarial disease, it is not always possible to say whether the splenic enlargement is entirely or partly attributable to the trypanosome.

Although, according to Greggio, trypanosome infection is not, as a rule, transmitted to the fœtus, the abortion-rate in the infected is increased from the normal 7 per cent. in Congo natives to 31·7 per cent., and the infant-mortality rate from 29 per cent. to 50 per cent. Trypanosomiasis in infants is extremely rare, though Kellerberger has recorded infection in an infant three weeks old.

Death from intercurrent disease, or from rapidly developing cerebral implication causing convulsions, the status epilepticus, coma, etc., may supervene at any stage of trypanosomiasis. Usually the case gradually drifts into the stage known as "sleeping sickness."¹ The incubation period may be a long one; among the slave-traders a period of seven years was regarded as being the limit.

Sleeping-sickness stage.—The terminal stage of trypanosome infection sometimes exhibits acute features, sometimes it is exceedingly chronic. While in a proportion of instances an interval of several years, possibly seven, may elapse from the commencement of the infection to the development of this terminal stage,

¹ It is customary to state that the development of the sleeping-sickness stage in trypanosomiasis concurs with and is dependent on the entrance of the parasite into the cerebro-spinal canal.

in the majority of cases the march of events is much more rapid. The characteristic terminal symptoms depend on implication of the nervous system either by the parasite itself or by its toxins.

According to Low and Castellani, the average duration of this stage of trypanosomiasis in the African is from four to eight months, not infrequently less; very chronic cases with a course of more than a year's duration are rare. Other observers refer to cases running on for three years, or even longer, and occasionally presenting temporary ameliorations.

Generally the first indications of the oncoming of sleeping sickness are merely an accentuation of the debility and languor usually associated with trypanosome infection. There is a disinclination to exertion; a slow, shuffling gait; a morose, vacant expression; a relaxation of features; a hanging of the lower lip; a puffiness and drooping of the eyelids; a tendency to lapse into sleep or a condition simulating sleep, the somnolence during the day-time contrasting with restlessness at night; a slowness in answering questions; a shirking of the day's task. Dull headache is generally present. Later there may occur fibrillary twitching of muscles, especially of the tongue, and tremor of the hands, more rarely of the legs, indicating a definite implication of the motor centres. By this time the patient has taken to bed, or he lies about in a corner of his hut, indifferent to everything going on around him, but still able to speak and take food if brought to him. He never spontaneously engages in conversation or even asks for food. As torpor deepens he forgets even to chew his food, falling asleep perhaps in the act of conveying it to his mouth, or with the half-masticated bolus still in his cheek. Nevertheless, such food as he can be got to take is digested and assimilated. Consequently, if he is properly nursed, at this stage there may be no general wasting. As time goes on he begins to lose flesh, tremor of hands and tongue becomes more marked, and convulsive or choreic movements may occur in the limbs or in limited muscular areas. (Fig. 32.) Sometimes these convulsions are followed by local temporary paralysis. Sometimes, too, rigidity of the cervical muscles and retraction of the head occur. There is usually an intolerable pruritus of the skin as originally observed by Manson in the first cases of the disease studied in England. Bedsores tend to form; the lips become swollen, and the saliva dribbles from the mouth. Gradually the lethargy deepens, the body wastes, the bedsores extend, the sphincters relax; and finally the patient dies comatose or sinks from slowly advancing asthenia. Possibly he succumbs to convulsions, hyperpyrexia, pneumonia, dysentery, or other intercurrent condition.

The manifestations described are subject to considerable variations. Thus, mania is not uncommon; delusions may present themselves, or psychical and physical symptoms not unlike those of general paralysis of the insane are developed. In the European, death is frequently due to convulsions, probably from the presence of the trypanosomes in the brain. Deep hyperæsthesia of the muscles is also quite common. The habits are usually bestial.

During the whole course of the nervous stage of trypanosomiasis the other symptoms already described as characteristic



Fig. 32.—Cerebral trypanosomiasis. Appearance of patient in last stages of the disease. (*Dr. F. K. Kleine.*)

of the infection may be in evidence. The knee-jerks, though lost towards the end, are active at first; the fundus oculi is normal; the sphincters, until towards the end, are controlled; the urine is normal, and the bowels, although generally tending to constipation, act with more or less regularity.

Complications.—In the Central African native the symptoms of trypanosomiasis are considerably aggravated by, and in many cases mistaken for, those of other diseases. The patient is invariably infected with malaria, ancylostomiasis, schistosomiasis, and possibly filariasis, besides which much of the emaciation, and the specific complications—septic rhinitis, otitis—are due to starvation and sheer neglect, as the patient, on showing symptoms of the disease, is usually expelled from the village by the inhabitants and left to die in the jungle, a terminal pneumonia or dysentery frequently supervening.

Mortality.—Although spontaneous recovery may take place in the early stages of trypanosomiasis, it is believed that when the disease has arrived at the stage of sleeping sickness, death is inevitable. Corre has told us how native villages in Senegambia have been depopulated. What has occurred on the Congo, in Angola, and in Uganda, bears out this estimate of the gravity of the disease when it appears in epidemic form. We know that many islands in the Victoria Nyanza have been completely depopulated. The population of the implicated districts of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping sickness.

Immunity.—Apparently man is immune to infection with the commoner trypanosomes of the big game, *T. congolense* and *T. vivax*, and also it is known that certain mammals are immune to trypanosomes which are pathogenic to others; thus *T. vivax* is pathogenic to horses and cattle, whilst rabbits, guinea-pigs, and mice are refractory. Although there is no direct evidence that man becomes immune after exposure to infection, yet there is no doubt that when the disease has lasted any length of time in a district, as in Southern Nigeria, the inhabitants exhibit a degree of resistance not seen in districts recently invaded.

The non-immune European generally suffers from the disease in a more acute form than does the Central African native under similar conditions.

Diagnosis.—Chronic irregular fever, more especially if associated with enlarged cervical glands and, in the European erythema multiforme, in a patient who has resided in tropical Africa at any time during the previous seven years, but more especially recently, suggests a tentative diagnosis of trypanosomiasis and detailed examination with this possibility in view. Diseases with which trypanosomiasis might be confounded are malaria, kala-azar, pellagra, syphilis, leprosy, and, in its later stages, beriberi.

The diagnosis of trypanosomiasis is made absolute, as already detailed, by blood examination. According to Morrison and Dye, the serum-formalin reaction (*see* p. 146) is usually positive in definite cases of trypanosomiasis and therefore serves as a rough guide for differentiation from other African fevers on a large scale. Davis and Brown have recently worked out a specific immunity reaction in trypanosomiasis known as the "adhesion phenomenon." The reaction is characterized by the adhesion to the parasite, when acted on by the immune plasma *in vitro*, of blood-platelets and other bodies. The reaction is specific for different species of trypano-

somiasis and the immune body shows a high degree of thermostability.

Malaria, syphilis, and leprosy are easily excluded. As regards *beriberi*, there should be no difficulty if it be borne in mind that it is a disease of the peripheral, while trypanosomiasis is a disease of the central nervous system; that *beriberi* is non-febrile and trypanosomiasis febrile. *Kala-azar* and trypanosomiasis, especially in their earlier stages, may be more difficult to differentiate, but the presence of enlarged glands, local œdema, and erythema multiforme in trypanosomiasis, and their absence in *kala-azar*, suffice for distinction. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish the diagnosis.

In *pellagra* the erythema is of a characteristic type. It is not ringed or fugitive as that of trypanosomiasis, and it affects principally the exposed parts of the body; the disease is of a much more chronic character, and, instead of lethargy, the mental condition, if implicated, is more that of insanity—melancholia alternating with mania and terminating in dementia. Further, in *pellagra* the symptoms are aggravated at particular seasons—spring and autumn.

General paralysis of the insane, cerebral tumour, forms of meningitis, especially encephalitis lethargica (often inaptly termed “sleepy sickness”), have features in common with trypanosomiasis and must be considered in diagnosis. The serum of some cases of trypanosomiasis has been said to give a positive Wassermann reaction.

The *microscopical diagnosis* of trypanosomiasis is sometimes difficult. Anæmia, as well as a large mononuclear leucocytosis, occurs in trypanosomiasis. A well-stained blood preparation exhibits, even to the naked eye, a remarkable clumping of the red corpuscles. Held up to the light, such a preparation has a peculiar granular appearance, produced, as can be seen on microscopical examination, by agglomeration of the corpuscles into heaps and clusters, the usual rouleaux arrangement being absent. This auto-agglutination of corpuscles is significant of, though not peculiar to, trypanosome infection. As a rule, the parasites in the peripheral circulation are few in number, many fields having to be hunted before a single example is discovered. Sometimes none can be found; rarely are they abundant. In the same case they are sometimes present, sometimes absent. Centrifuging citrated blood may prove of considerable assistance. Broden uses 9 c.c. of blood to 1 c.c. of 6-per-cent. citrate solution, centrifuged at first

at 1,000 and subsequently at 1,500 revolutions for 10 minutes. The supernatant fluid of the latter is again centrifuged at 2,000 revolutions for 20 minutes, when the trypanosomes will be deposited. Letonturier, Tanon and Jamot consider that this triple centrifugation method gives 92 per cent. of positive results.

Dutton and Todd have emphasized the value of *lymph-gland puncture* and examination of the aspirated lymph as the most certain method, particularly in the earlier stages of the disease, when the glands are soft and the trypanosomes abound in the lymph, before they have become sclerosed. This method is said to succeed in 87·7 per cent. of cases. An ordinary hypodermic syringe suffices to aspirate a sufficiency of lymph, of which films are prepared and stained in the ordinary way. According to Kleine's statistics, out of 32 patients 24 had trypanosomes in their glands and blood, 4 had them in the glands but not in the blood, and 4 had them in the blood only. On the other hand it must be emphasized that gland-puncture is not infallible, as a percentage of those infected fail to develop a lymphatic reaction. Gland-puncture as a means of diagnosis should always be reinforced by the examination of thick blood-films. *Cerebro-spinal fluid*, obtained by lumbar puncture and centrifuged, affords another, though not always a practicable, means of finding the parasite; according to Broden, parasites may be demonstrated in this manner in 4·5 per cent. of cases, but if the trypanosome is not found, suggestive information may be obtained from a lymphocyte-cell count of the fluid, as this may be increased to over 1,000 per c.mm. The globulin content of the fluid is also augmented.

Failing discovery of the parasite by blood or lymph examination, recourse must be had to *animal inoculation*, 2–10 c.c. of the former being drawn from a vein and injected. Of the ordinary laboratory animals, the most susceptible, and therefore most reliable, are the guinea-pig, the rat, the dog, and certain monkeys, *Macacus* and *Cercopithecus*. Such inoculations are of value as a test of recovery, as well as for diagnosis.

The trypanosome is easily stained by most dyes, those in use for malaria work giving the best results. A $\frac{1}{8}$ -in. objective suffices to find the parasite.

Treatment.—Especially in the case of natives, preliminary treatment directed towards the eliminating of superimposed infections with ancylostomes or schistosomes is always advisable, especially on account of damage to the liver-cells which renders toleration of arsenical drugs difficult. The exhibition of glycerophosphates at this stage, for repair of nervous tissue, is indicated.

Although something may be done to relieve symptoms and delay the fatal issue in the sleeping-sickness stage, it is only in the earlier stages of the infection and by the persistent and energetic use of "Bayer 205," tryparsamide, arsenic, or antimony, single or combined, that a cure can be effected, and that in a proportion of cases only. Other drugs have been shown to have some influence on the trypanosome infections of the lower animals, but their therapeutic value in those of man is practically negligible.

Arsenic.—The effects of the administration of arsenic compounds on a heavily infected animal are very marked; after a preliminary and pronounced increase, the number of parasites in the peripheral circulation is reduced.

Atoxyl (or *soamin*), a meta-arsenic-anilin compound, introduced by Thomas, has one serious drawback—in large doses it is apt to give rise to optic neuritis, and consequent atrophy and blindness. The drug, therefore, must at once be stopped on the slightest threatening—dimness of vision or congestion of the disc—of such a calamity. Gastro-intestinal irritation and peripheral neuritis are also indications that it has to be suspended, at least temporarily, and the subsequent dosage reduced.

Atoxyl is best given intramuscularly in 10-per-cent. solution in sterile normal saline. The solution should be freshly made and free from precipitate. The individual dose should not exceed 7 gr. The practice as regards dosage and the times and frequency of administration varies. Some advocate a 7-gr. dose once every fifth day until symptoms subside. After a few weeks, similar courses, lasting for a month, and repeated at short intervals, are kept up for at least one year. Manson's practice was to give an injection of 3 gr. every third day, and to keep this up uninterruptedly for two years, unless symptoms of arsenical poisoning showed themselves, when the course was temporarily intermitted.

A serious objection to the continued use of atoxyl is the liability of the trypanosomes to become resistant or "fast" to this drug. The repeated injection of atoxyl, insufficient to prevent a relapse in mice, finally results in a strain of trypanosome being evolved which is quite unaffected by the drug.

Tryparsamide, the sodium salt of N-phenylglycineamide-p-arsonic acid, was introduced for the treatment of trypanosomiasis by Drs. W. H. Brown and Louise Pearce, of the Rockefeller Institute. The preliminary experiments on laboratory animals were very encouraging, and further work on the Congo has strengthened the belief that in this drug we possess a potent trypanicide. The drug is a white powder very soluble in water. When injected into the tissues it is quickly absorbed; it may be given by either the intramuscular or the intravenous route. The individual doses are large, varying from 1 to 4 grm.; the optimum dosage is about 83 mg. per kilo of body-weight. The drug has a marked effect upon the symptoms of the disease, especially when the nervous system is involved; the trypanosomes, when present in the cerebro-spinal fluid, disappear; and furthermore there is a

great reduction in the round cells or lymphocytes in this fluid in cerebral trypanosomiasis, which is attributed to the high degree of penetrability that the drug possesses; it is apparently capable of entering the brain substance, and possibly also of finding its way into the cerebro-spinal fluid. In an average case the initial dose should be 1 grm. in 10 c.c. of distilled water; subsequently it may be given in 2-grm. doses, three times weekly. A total dosage of 24 grm. is, as a rule, necessary.

Tartar emetic injections are now mostly used to reinforce tryparsamide treatment in cases complicated by schistosomiasis. It has also been employed effectively in conjunction with Bayer 205.

According to Chesterman, who has had a large experience of tryparsamide, the intravenous route is the most effective: the solution should not exceed 40 per cent., which is about the saturation point. Care should be taken to see that the water is not alkaline in reaction as this produces precipitation. Intramuscular injection is also efficacious, but the solution should not exceed 20 per cent. Experience has proved that it is not wise to attempt "*therapia sterilisans magna*," as prolonged administration of the maximum tolerated dose gives the best results.

In early cases in adults a start should be made with 0.04 grm. per Kg. of body-weight and continued for a total of twelve weekly injections. Children up to twelve years of age, on the other hand, tolerate the drug well and should be given double this dose up to 0.08 grm. per Kg. of body-weight for twelve injections. A second course should be given as for adults.

Results of treatment with tryparsamide.—In early cases an apparent cure is almost invariable, but tryparsamide acts less certainly after prior administration of atoxyl or other arsenicals. In later cases figures vary, but given good conditions in the absence of other debilitating diseases, cases in which the degeneration of the central nervous system has not progressed too far and when the cerebro-spinal fluid does not contain too many cells the drug gives gratifying results.

In more *advanced cases* in adults smaller doses up to 0.02 grm. per Kg. of body-weight should be given, on the fourth day 0.03 grm. per Kg., and on the eighth a course of 20 injections of 0.04 grm. per Kg. should be commenced. The course of ten injections should be repeated three months after the first. For children one should use doses of 0.06 grm. per Kg. If the drug is used in strengths of more than 20 per cent. by the intramuscular route, induration of abscesses results. In later cases a Herxheimer reaction with acute mania may ensue should the initial dose too be large. Optic neuritis must be carefully watched for; visual symptoms may appear after the third or fourth dose, but generally not till later. Premonitory symptoms are photophobia, lacrymation, pain in the eyes and dimness of vision. It should be made the rule to test the vision of each patient before injection by detection of some small object. In any suspicious case the administration of arsenicals should be suspended and replaced by tartar emetic for one month, but the total course of tryparsamide should be completed if possible. Injections of sodium thiosulphate may be given, though they do not apparently hasten recuperation. It must be remembered that the action of arsenic is often a delayed

one and the symptoms of optic neuritis may progress even after cessation of arsenic treatment.

As a criterion of cure in addition to the physical improvement in the patient and in his mental capacities a normal cell-count and albumin content of the cerebro-spinal fluid should be maintained for twelve months after treatment and should be regarded as sufficient evidence of cure after the cessation of treatment; an excess of albumin, as well as of cells, may be noted for a short time, but disappear later.

The doses of tryparsamide for intramuscular injection are the same as those employed for intravenous. According to King, it should be given in 20-per-cent. solution when no local reactions occur. The results are similar to those of the intravenous method, but not so lasting.

N-phenylglycineamide-p-arsonic acid, of which tryparsamide is the sodium salt, may be given by the mouth which, in dealing with large numbers of natives, is a simpler method. In contrast to tryparsamide it is well tolerated by this route and causes disappearance of trypanosomes from the blood and cerebro-spinal fluid though in a slower and less dramatic manner. The tablets (supplied by Messrs. May and Baker) are crushed in water and swallowed. The dosage is twice that of tryparsamide by the parenteral route and has the advantage of being less liable to produce optic neuritis, any excess manifesting itself in gastro-intestinal irritation and elimination of the arsenic through diarrhoea.

Antimony, in the form of sodium- or potassium-antimony-tartrate, was formerly given intramuscularly in 1-gr. doses; it caused great pain. It is necessary to commence with $\frac{1}{2}$ gr. dissolved in 10 c.c. of sterile distilled water and injected directly into a vein; this dosage should be increased by $\frac{1}{2}$ gr. on each occasion till a limit of 2 gr. as an individual dose is reached. It is advisable to give the injection on alternate days, as in schistosomiasis (p. 520); should a small quantity of menstruum be used, the resulting reaction is less severe. Most clinicians prefer to inject it direct into the vein by means of a 10 c.c. Record syringe.

As with atoxyl, there were differences in the method of employing antimony injections. Some gave them on alternate days; others, twice weekly; yet others, once a week. After the short fever which may ensue, the administration of antimony is usually followed by marked relief of symptoms. As regards the total quantity to be given by this method, no rule can be laid down; generally it amounts to well over 50 gr.

Other forms of antimony treatment.—In view of the irritating effects of antimony, antimony trioxide may be injected subcutaneously in the form known as *Injectio-antimonii-oxidi* (Martindale), which contains a solution of the drug in equal parts of glycerin and water, 1 c.c. of the solution containing $\frac{1}{10}$ gr. of trioxide of antimony: 1–2 c.c. of this preparation can be injected subcutaneously or intramuscularly without any ill effect. Being painless and easily tolerated, it can be used as an adjuvant of, but not as a substitute for, antimony tartrate injected intravenously.

Combined arsenic and antimony treatments.—As pointed out by Ehrlich, certain strains of trypanosomes become “arsenic-fast,” that is, they resist the action of the drug—a property which becomes hereditary, and is continued in subinoculations into the lower animals; and the same thing takes place with regard to antimony. This undoubtedly accounts for the failure of arsenical and antimony treatment in a large proportion of cases. As the atoxyl-fast trypanosomes may respond to antimony, and vice versa, both drugs may be employed.

Bayer 205 (Germanin).—This drug was introduced by Messrs. Bayer and Co. in 1920; its therapeutic properties as applied to trypanosomiasis in man were foreshadowed by its remarkable trypanicidal action in laboratory animals. The drug is a white powder of unknown composition;¹ it is easily soluble in water and is probably a pure aniline compound.

In animals the drug has been found remarkably non-poisonous. The *dosis tolerata* has been estimated to be 160 times that of the *dosis therapeutica*. In animals the drug, injected either subcutaneously or intravenously, is lethal to *T. brucei*, *gambiense*, and *rhodesiense*, and has been found to exert a feeble prophylactic action. In man, cures have been reported by Mühlens and Menk, Kleine and Fischer, Low and the Editor. The dose for man is 1 gm. dissolved in 10 c.c. of distilled water. The total amount required is about 10 gm.; the trypanosomes have been observed to reappear after 5 gm. They disappear from the peripheral blood about twelve hours after the injection, and the injection should be repeated at weekly intervals. Fischer believes the best results are obtained by the injection of more intensive initial doses—1 gm. on the first, third, tenth and thirteenth days—and that in natives a total quantity of 5 gm. is sufficient to eradicate the infection.

The blood-serum, cerebro-spinal fluid, and urine of the patient subsequent to treatment with "205" possess trypanicidal action when injected into infected mice. The improvement in the physical condition and mental outlook of the patient after injection is remarkable. The drug apparently has a cumulative action and is an irritant to the kidneys, so that after three or four injections albuminuria with the passage of small granular casts almost invariably occurs, though the damage to the kidneys, lasting about six weeks, is not permanent. In animals it acts effectively when given by the mouth, but, as yet, evidence is lacking that, administered in this way, it has a similar therapeutic action in man. It is now recognized that "205" is one of the most active substances yet employed in the treatment of sleeping sickness, for it has been shown to cure cases in which all other known forms of treatment had failed. Whether it is capable of destroying the trypanosomes when once they have entered the grey matter of the brain is doubtful. Kleine and Fischer have now reported on the treatment of 185 cases

¹ According to Fournéau, Tréfouël, and Vallée, the chemical composition of "205" is that of a symmetrical urea of acid meta-aminobenzoyl-meta-aminopara-methylbenzoyl-i-naphthylamino—4-6-8—trisulphate of soda. They have synthesized, under the designation of "309," a preparation which has the same physical and therapeutic properties as "205."

in Africa, of which 80 per cent. showed very marked improvement and were considered as cured.¹

It is difficult to reconcile the claims made for the results of treatment in different parts of Africa for Bayer 205 and for tryparsamide. It is probably correct to state that Bayer 205 has a remarkable sterilizing effect during the early hæmic stages of infection, but has little or no action when involvement of the nervous system has taken place. It is probably more effective in *T. rhodesiense* infections than *T. gambiense*. Bayer 205 is often effective in cases which do not respond to tryparsamide and in which the trypanosomes have become arsenic-fast. There is a certain amount of evidence that alternating treatment with both drugs is most effective, though Chesterman has pointed out that the renal damage caused by Bayer 205 is more likely to produce optic neuritis in those subsequently injected with tryparsamide.

Prophylaxis.—The indications for prophylaxis are based principally on the habits of *Glossina palpalis*, and the existing conditions as regards the presence of the infection in a locality.

In endemic regions the fly areas should be located and avoided. If such regions have to be traversed, the journey should be made during dark nights, when tsetse-flies do not feed, or with such precautions as are used by the natives for the protection of their cattle in nagana-infected spots. Those who are compelled to live in tsetse regions should have their houses and persons carefully guarded against the fly. Manifestly, it is desirable—whether it is feasible is another question—to avoid localities in which the natives are affected, and to prevent infection of the local tsetse-flies by people who have trypanosomes in their blood, by means of mosquito-netting, or by other measures, such as removing them from the usually very limited fly area to some neighbouring fly-free spot. Movement of infected individuals to hitherto uninfected countries must necessarily be attended with great risk of the introduction of the disease. Whether such movement can be prevented in savage lands depends greatly on local circumstances. Wherever possible it should be prevented. Dutton and Todd suggest that an easily ascertained condition, more or less general in trypanosomiasis—namely, enlargement of the cervical glands—should be employed in eliminating dangerous individuals. Many years ago slave-dealers adopted such a method to shield

¹ So far the prophylactic action of this drug in animals under natural conditions has proved disappointing; it does not prevent infection with trypanosomiasis, but, according to Kleine, it does definitely mitigate the pathogenicity of the infecting virus; prophylactically-inoculated animals remain in good health and condition on subsequent infection with *T. brucei*.

themselves from loss. As a rough test it has some value. But in some cases of trypanosomiasis the glands are not appreciably enlarged at all times. Moreover, as they are often enlarged in other conditions, injustice might be done in enforcing such a measure.

Hodges and his colleagues in Uganda inform us that the fly ground proper is always a very narrow strip, not more than ten to fifteen yards wide, and always along the water's edge, and that the insects very rarely extend their feeding beat sixty yards beyond this, whether on the land side or on the water side. It is true they may follow with great persistency a man who has just passed through this narrow belt, for several hundred yards, rarely for half-a-mile; but it is obvious that if the ten or fifteen yards at the water's edge be made unsuitable for the fly, as can be done by clearing it of jungle, there will soon be no flies to follow human beings, and the place will become safe. Therefore, where feasible, fly spots, where there are landing-places, ferries, wells, or roads, should either be avoided altogether or be cleared of jungle for some yards—to be safe, thirty—from the water's edge. This is a practicable measure of proved value in Uganda.

Brilliant results have attended the efforts of the Portuguese to combat sleeping sickness in the island of Principe, where the annual mortality from the disease amounted to 83 per thousand of the population, and the local industry (cocoa) was threatened with extinction. Besides jungle-clearing, drainage, blood examinations and segregation of the infected, and destruction of possible animal reservoirs of the trypanosome, coolies, dressed in white and carrying on their backs a dark cloth smeared with birdlime, were sent into the jungle, and every night the flies caught were removed and counted. In three years 470,000 glossinæ were caught. As a consequence of this combination of sanitary measures the fly and the sleeping sickness were exterminated. Of course, it was only the complete isolation and the limited size of the island that made such a result possible.

A complete scientific prophylaxis can be indicated with certainty only when we have full knowledge (1) of the habits of the tsetse-flies and of the reasons for their restriction to very limited and apparently capriciously distributed areas; (2) of what vertebrates under natural conditions are normally hosts of *T. gambiense*. Experiment has shown that the glossina will bite any vertebrate, and that it can infect a large variety of mammals with the trypanosome. If this be the case in the laboratory, it is reasonable to suppose that it obtains in nature also. Therefore, in the endemic regions of trypanosomiasis the vertebrate fauna has to be reckoned with as

a source and reservoir of infection. Domestic animals probably do not constitute a serious source of infection. Duke has shown that the transmissibility of a strain of *T. gambiense* diminishes when the strain is introduced into a sheep or a goat.

Attempts recently made by Lamborn to introduce a predatory insect which would destroy the pupæ of Glossina have so far been attended with but a moderate degree of success. In 1914 Austen suggested the introduction of the chalcidid—*spalangia*—into tracts where *G. morsitans* is a pest. Consequently one species of Chalcidiid *Syntomosphyrum glossinæ* has been bred in large numbers in the laboratory and distributed over an area of Lake Nyasa of about 42 square miles. In the course of three months it was found that 8·7 per cent. of glossina pupæ were parasitized by *syntomosphyrum*.

In Uganda and elsewhere, principally in order to preserve the hitherto uninfected from trypanosome infection, the Government removed the entire population of the Sesse Islands and neighbouring shore of Lake Victoria Nyanza to fly-free areas in the interior. It was hoped that, the human source of trypanosome supply being thus denied them, the tsetse-flies would cease to be infective. Unfortunately, this hope has been disappointed. Three years after the depopulation of the districts involved, Bruce ascertained that local flies could still convey the disease to laboratory animals. Manifestly, *T. gambiense* can flourish under natural conditions in vertebrates other than man, especially in the situtunga antelope.

The introduction of *T. gambiense* into other countries is a grave possibility. It is true that it must have been frequently introduced into America in the days of slave importation and that it did not spread there; but as regards India and other Asiatic countries, which hitherto have had little or no communication with the West Coast of Africa, no introduction on a large scale has occurred, and we have no assurance that, if introduced, the parasite would not find some appropriate transmitter. Furthermore, the possibility of the introduction of the fly host of the trypanosome of sleeping sickness, *G. palpalis*, into other tropical countries must not be lost sight of.

[For a detailed description of the tsetse-flies (Plate IX), see p. 823.]

RHODESIENSE SLEEPING SICKNESS

The trypanosome found in cases of human sleeping sickness originating in Rhodesia was, until recently, considered to have certain peculiarities when inoculated into the rat. This fact, together with the greater virulence of the disease as it occurs both in man and in laboratory animals, and the greater resistance

this trypanosome exhibits to arsenical treatment, led Stephens and Fantham to separate it as a distinct species under the name of *T. rhodesiense*, in 1910. Later, it was proved that the parasite is transmitted by *Glossina morsitans* (Kingshorn and Yorke), not by *G. palpalis*. Until recently some authorities regarded *T. rhodesiense* merely as a human strain of *T. brucei*, the common parasite of big game.

The status of *T. rhodesiense* as a species distinct from *T. gambiense* has been severely shaken by the evidence of the International Commission on Human Trypanosomiasis recently published. The conclusion reached by the Commission tends to show that *T. rhodesiense* and *T. gambiense* are identical; in other words, *T. rhodesiense* is merely *T. gambiense* which has been transmitted through a different species of glossina—viz. *G. morsitans*.

Geographical distribution.—This form of sleeping sickness occurs in North-Eastern Rhodesia, especially in the Luangwa Valley, about the southernmost limit, 14° S.; in the south-eastern portions of Tanganyika Territory up to 10° S.; in Portuguese East Africa; in Nyasaland, especially in the region south and west of Lake Nyasa; in fact, its distribution closely corresponds with that of *G. morsitans*.

Etiology.—In human blood (Fig. 33-1, 2), *T. rhodesiense* is morphologically indistinguishable from *T. gambiense*; but if it is passed through the rat or guinea-pig, a small but variable proportion of the parasites, especially the stumpy forms, will be seen to have their nuclei located posteriorly to the kinetoplast—that is to say, at the non-flagellar end of the organism. (Fig. 33-3, 4, 5, 6.) According to Kleine and Lavier of the International Commission, posterior-nucleated forms are found in the blood of guinea-pigs inoculated with *T. gambiense*. Until this work has been confirmed it would be as well to suspend judgment upon the duality of these two species.

A good deal of energy and work have been expended in attempting to prove and disprove that *T. rhodesiense* is no other than a strain of *T. brucei* inoculated into man. When injected into rats, *T. brucei* exhibits the same proportion of posterior-nucleated forms as *T. rhodesiense* (Bruce). Taute and his fellow-workers have disproved this theory somewhat conclusively by inoculating themselves and 129 native porters with dog's and mule's blood containing *T. brucei*—with a negative result, while rats, dogs and a goat inoculated with the same blood at the same time, succumbed. These experiments, they claim, definitely disprove that *T. brucei* is in any way pathogenic to man.

RESERVOIR-HOSTS

Three species of antelope, the waterbuck, reedbuck, and duikerbuck, are usually regarded as reservoir-hosts of the *rhodesiense* form. The common waterbuck has been artificially infected with the human *T. rhodesiense*, and though they themselves show no signs of disease it has yet been proved that their blood is infective to monkeys (Week).

The outbreaks reported by Duke and Swynnerton near Mwanza in 1922, and by Dye in the south-eastern districts of Tanganyika Territory in 1927, render it probable that in these instances the so-called *T. rhodesiense* was conveyed directly from man to man by *Glossina swynnertonii* without the intervention of any big game.

Symptoms are similar to those evoked by *T. gambiense*, though febrile paroxysms are more frequent, and severe glandular enlargement is not often met with. The disease generally runs a much more rapid course, and fatal symptoms usually supervene within a year of infection, death taking place from convulsions. Acute mental symptoms, such as mania, are frequently observed.

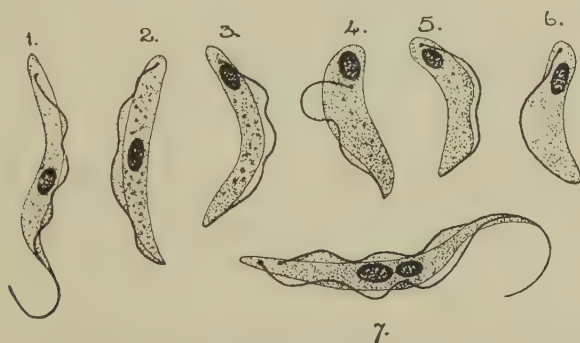


Fig. 33.—Forms of *Trypanosoma rhodesiense*. (After Laveran.)

1, 2, Normal forms in blood of man; 3-6, various stages of posterior displacement of the nucleus; 7, a dividing form.

Diagnosis is the same as for *T. gambiense*. Possibly the parasites are more easily demonstrated by lymphatic gland puncture. Dye considers the serum-formalin reaction of some value, though it does not appear to be by any means as specific as in kala-azar.

TREATMENT

Atoxyl, tryparsamide and antimony preparations (see pp. 117-119) which are of use in *T. gambiense* infections appear to be relatively powerless in *T. rhodesiense* cases. Successes have been reported after massive intravenous doses of antimony tartrate when treatment is commenced early and a total of over 500 gr. has been administered (Daniels and Newham). Unfortunately, some of the apparently cured cases which have been recorded have subsequently relapsed.

The treatment with Bayer 205 (*Germanin*) is much more hopeful; a few remarkable successes having so far been recorded, in fact the drug appears to exert a much more immediate and specific action than in *T. gambiense* infections. Dye in Tanganyika Territory reports that intravenous injections on the first, third and

fifth days, subsequently at intervals of five to seven days till a total of 7 grm. has been administered, resulted in the disappearance of the trypanosomes from the peripheral blood within twenty-four hours. The drug no doubt has a remarkable sterilizing effect in early hæmic infections. The Editor has had two striking examples in young Europeans, both of whom were permanently cured with 2 grm. of Bayer 205 given within fourteen days from the time the infection was detected. One had entirely failed to respond to tryparsamide (Milne Tough). The latter drug has no action on *T. rhodesiense* comparable to *T. gambiense* infections (Dye).

There is some evidence that in man a strain of Bayer 205-fast trypanosomes may be evolved, as Morgenroth and Freund have shown takes place in mice, and Kleine and Fischer in monkeys and cattle. One European case under the Editor's care relapsed and died after 33 grm. of Bayer 205 had been injected, and the trypanosomes reappeared in the blood and cerebrospinal fluid apparently uninfluenced by the drug.

Prophylaxis.—Prompted by the results of his investigations of the hypothesis that the big game act as a reservoir for *T. rhodesiense*, Yorke has advocated the extermination of this fauna, but recent investigations tend to show that these conclusions were premature and that man himself is the chief source of infection.

Note to the student.—As the prophylaxis of trypanosomiasis is interwoven with a knowledge of the life-history of the tsetse-fly and its breeding habits, the student is referred to the section on Entomology where this subject is dealt with (p. 823).

It is also necessary that he should have a working knowledge of the appearance and pathogenic properties of trypanosomes which are morphologically similar to those found in man (*see* p. 686).

II. SOUTH AMERICAN HUMAN TRYPANOSOMIASIS

Synonyms.—*Chagas' Disease*; *Derrengadera*. Native names, "Opilacão," "Canguary" (Brumpt).

Definition.—This is usually an acute, and more rarely a chronic disease, caused by *Trypanosoma* (*Schizotrypanum*) *cruzi*, and disseminated by certain reduviid bugs. The acute stage of the disease is characterized by diarrhœa, enlargement of the lymphatic glands, the thyroid, and the spleen, accompanied by cerebral symptoms. The chronic form is marked by special symptoms, according as the heart or other important organs are most invaded by the parasite.

History.—In 1909 Cruz and Chagas found a form of trypanosomiasis in children in Brazil; at the same time they traced the development of *T. cruzi* in the reduviid bug *Triatoma megista*, which transmits the disease

to man and domestic animals, although allied species of bug, and even arthropods, have been found by Brumpt to have the power of transmitting the infection, at any rate under experimental conditions.

Geographical distribution.—In the provinces of Minas Geraes, Sao Paulo and Goyaz in Brazil; in the states of Trujillo and Miranda¹ in Venezuela, in San Salvador (Segovia), and in the Argentine in Tucuman and Jujuy (Mühlens). (Map I.)

That this trypanosome is probably a more frequent infection than has hitherto been suspected, is shown by the fact that Noguchi (1924) records the isolation of a trypanosome from the blood of a yellow-fever patient.

Trypanosoma cruzi, or trypanosomes resembling it, have been found in bugs (*Triatoma* and *Rhodnius*) in the Argentine and in California, but they do not transmit the disease to man in these regions.

Etiology.—During the febrile attacks the parasite, *T. cruzi*, can be found only sparingly in the blood, though in the acute disease, as seen in children, it is more abundant. In chronic cases, in which the clinical symptoms may be puzzling, they are apparently absent.

This trypanosome was at first referred to a separate genus, *Schizotrypanum*, on account of its distinctive method of multiplication in the human body. In place of the longitudinal division which occurs in other species of trypanosomes, this parasite proliferates in the cells of the internal organs, especially in the interior of striated muscles, such as the heart. Two forms, one slender, the other broad, are met with in the peripheral blood. In the internal organs multiplication takes place by schizogony (Fig. 34) at a very rapid rate, the resulting forms resembling leishmania bodies, which, four days later, become transformed once more into trypanosomes that invade the blood-stream. (For complete development of the parasite, see Appendix p. 684.)

T. cruzi is easily cultured on N.N.N. medium, in which it assumes the stunted forms usually seen when it is found in its definitive hosts.

The reservoir-hosts of *T. cruzi* are animals peculiar to the country in which the disease occurs; these are various species of armadillo and opossum.

Transmission.—The adult trypanosomes are ingested by the intermediary invertebrate host, *Triatoma megista*,² either in the larval, the nymphal, or the adult stage of this bug. After they

¹ One case of human trypanosomiasis has been reported from Peru (by Escomel).

² This bug has been given various synonyms at various times, and is described in the literature as *Lamus megistus* and *Conorhinus megistus*.

have passed through many stages in the intestinal canal, in a period of 8-10 days fully formed trypanosomes known as "metacyclic" forms reappear in the hindgut and are passed out through the fæces of the insect. Infection of man, therefore, probably takes place through the insect defæcating into the wound caused by its bite. The original idea of Chagas (1909) that infection is conveyed by the bite of the triatoma has not been confirmed. Mayer has recently stated that infection may be conveyed hereditarily through the bug.

Under experimental conditions, all laboratory animals can

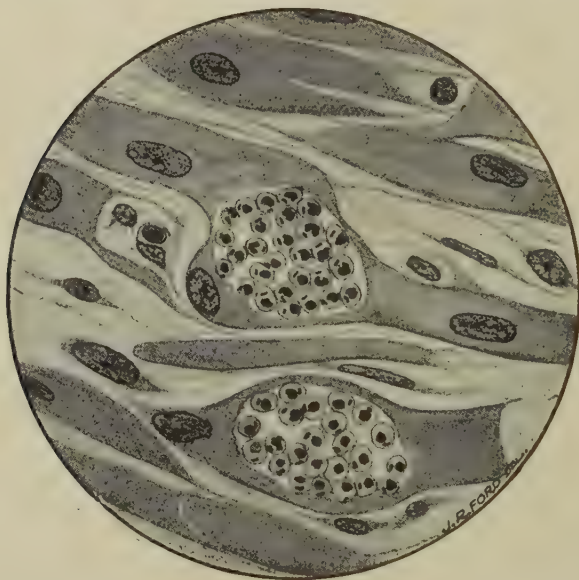


Fig. 34.—*Trypanosoma cruzi*: schizogony in heart-muscle.

(From a preparation by J. Gordon Thomson.)

be readily infected, and under natural conditions the domestic cat has been found to harbour this trypanosome. The parasite is capable of developing in a number of species of *Triatoma* and allied genera (*Rhodnius* and *Erathyrus*). In infected animals transmission of the trypanosome from the parent to the offspring *in utero* can apparently take place (Chagas).

Pathology.—The post-mortem appearances in man have been described in children dying of this disease. There is enlargement of the spleen, parenchymatous degeneration of the liver, and general enlargement of the mesenteric glands. The thyroid gland,

as a general rule, is congested and hypertrophied. There is general infiltration of the subcutaneous tissues and thickening of the serous membranes. Subserous ecchymoses are common, and small hæmorrhages in the brain and spinal cord have been described. The gross lesions in the various organs are due to the presence of the parasite. Under the microscope, cyst-like cells can be found, particularly in the striated muscular fibres, and in those of the heart. When the suprarenal gland is affected, pigmentation of the skin and other evidence of Addison's disease have been observed. The blood does not show great changes, as a rule, and the trypanosome may persist without causing severe anæmia for a very long period. Trypanosomes have been found in the blood of a man 25 years of age, who exhibited no marked symptoms of disease.

Symptoms.—(a) *The acute form* usually occurs in infants of about one year. A fever exhibiting slight nocturnal elevations persists as long as the parasite occurs in the blood. In very severe cases it may reach 104° F. There is often a general anasarca. The face is puffy, the thyroid gland greatly hypertrophied, and the superficial lymphatic glands, especially the axillary and inguinal, are enlarged. The puffiness of the face, accompanied by conjunctivitis, is said to be so characteristic as to be almost diagnostic of the disease, and on this account it was formerly confused with ancylostomiasis in children. The liver and spleen are both enlarged. The thyroid enlargement is one of the earliest symptoms, and has been observed in breast-fed children 2–3 months old. In the terminal stages the child develops symptoms of an acute meningo-encephalitis; death generally takes place within a month of the onset, but should the child survive, the disease passes into the chronic form.

(b) *The chronic form.*—According to Brumpt, Chagas' disease in the chronic form may be subdivided into the following varieties, viz. pseudo-myxœdematous, myxœdematous, cardiac, and nervous. The pseudo-myxœdematous type is frequent in children up to 15 years of age; they suffer from a chronic cachexia, irregular fever, cardiac hypertrophy, and tachycardia. There are usually other myxœdematous symptoms as evidenced by the infiltration of the subcutaneous tissues, and bronzing of the skin, resembling Addison's disease. The spleen, liver, and lymphatic glands are enlarged, as well as the parotids on rare occasions; epileptiform convulsions may occur.

The myxœdematous type is characterized by great thyroid insufficiency, scanty secretion of urine, dry skin, etc. These cases resemble classical myxœdema.

The cardiac type is characterized by cardiac arrhythmia. The frequent occurrence of extrasystoles produces a disturbance of the cardiac rhythm, which becomes especially marked on lying down. A bradycardia of 24 beats per minute has been observed in these cases (Chagas). Pericarditis may supervene, and is usually fatal.

The nervous type is characterized by "intention tremor," various paralyses, muscular contractions, and choreic movements. The brain and cranial nerves may be involved, producing various types of aphasia. Cerebral diplegias, ending in infantilism and mental deficiencies, as a result of this disease, have been described.

It is only fair to state that not all authorities are agreed that the above description is distinctive of Chagas' disease. It has been pointed out, notably by Kraus, that it is difficult to distinguish endemic goitre and cretinism from the clinical picture of acute and chronic trypanosome infection as depicted by Chagas. According to Munk, in the district where Chagas made his discovery, 75 per cent. of the indigenous population have goitre, and a cretin is found in almost every family.

Diagnosis.—The trypanosome is usually present in very small numbers in the blood-stream, and prolonged search may be required for its detection. It may be necessary to collect the blood in citrated saline, and subject it to prolonged centrifuging. The parasites may sometimes be found in the cerebro-spinal fluid by lumbar puncture; on the other hand, puncture of the lymphatic glands seldom reveals the organisms. A readier method of diagnosis consists in inoculating a guinea-pig with the patient's blood, when the developmental stages of the parasite may be found subsequently in the organs of this animal. In the acute form it is said that positive results are obtained by inoculation of guinea-pigs in 26 per cent. of cases. In chronic cases animal inoculation is negative. These difficulties in diagnosis have led to the elaboration of a complement-fixation test (Villela and Bicalho). The antigen is prepared from a glycerin extract of heart and spleen of infected animals. The specificity of the test must be accepted with reserve as regards other forms of human trypanosomiasis.

Brumpt has suggested a method of xeno-diagnosis which consists in feeding laboratory-bred triatomas with the blood of the suspected person, when the cyclical development of the trypanosome can be readily demonstrated in the intestinal tract of the insect.

On clinical grounds, Chagas' disease is to be distinguished from endemic goitre, ancylostomiasis, Graves's disease, cretinism, myxœdema, Addison's disease, and other disturbances of the endocrine glands.

Treatment.—Unfortunately, arsenical and antimony compounds employed in the treatment of the other forms of trypanosomiasis have been found by no means so effective in Chagas' disease. The new drug Bayer 205 has no effect upon it. In the myxœdematous forms, thyroid medication should prove beneficial.

Prophylaxis.—This should be directed principally to the suppression of the insect concerned—*Triatoma megista* (Fig. 368). It is a large black insect belonging to the family Reduviidæ, well known to the natives, who call it "barbeiro." The nymphs bite and can convey the infection, but the adults, having wings, are more dangerous. In the daytime they live in the grass walls and roofs of the dirty native houses, or of pigsties, coming out after dark in search of their food—blood. Their habits indicate better and cleaner housing, sleeping off the ground, and protection by mosquito-netting.

The fact that the armadillo is the reservoir-host suggests that human habitations should be placed as far away from the burrows of these animals as possible, and that the floors of the houses should be constructed so that the armadillo cannot burrow underneath them. Brumpt has called attention to the fact that one form of the triatoma, *T. geniculata*, which normally feeds on the armadillo, is commonly met with in the burrows of a rodent, *Cherodon rupestris*, and that the trypanosome can be found in these bugs at great distances from any human habitation. It is, therefore, possible that the disease exists independently of man.

ANIMAL RESERVOIR-HOSTS

The most important reservoir-host is the armadillo which is distributed throughout South America and is frequently found in burrows in the vicinity of human habitations. In these situations too, the *Triatoma* (*T. geniculata* and *T. megista*) is at home. When the armadillo abandons its burrow the bugs migrate, sometimes to human habitations. In the armadillo the trypanosome is found in the same situations and produces the same lesions as in man. The long-tailed armadillo (*Tatusia novemcincta*) is the commonest species, abounding in Guatemala up to altitudes of 5,000 feet. The flesh is much esteemed by the natives. The "peludo" (*Dasypus sexcinctus*) is a much smaller animal, 18 in. in length. It is specially common in Brazil and feeds to a great extent on carrion. One other species of armadillo *D. unicinctus* is also suspected.

CHAPTER IV

LEISHMANIASIS

UNDER the term Leishmaniasis at least three diseases are included—Kala-azar, Oriental Sore, and Espundia. (Map III.) These diseases, though clinically quite distinct and having each a definite topical and geographical distribution, are all associated with what optically appears to be the same organism, *Leishmania*.

I. KALA-AZAR

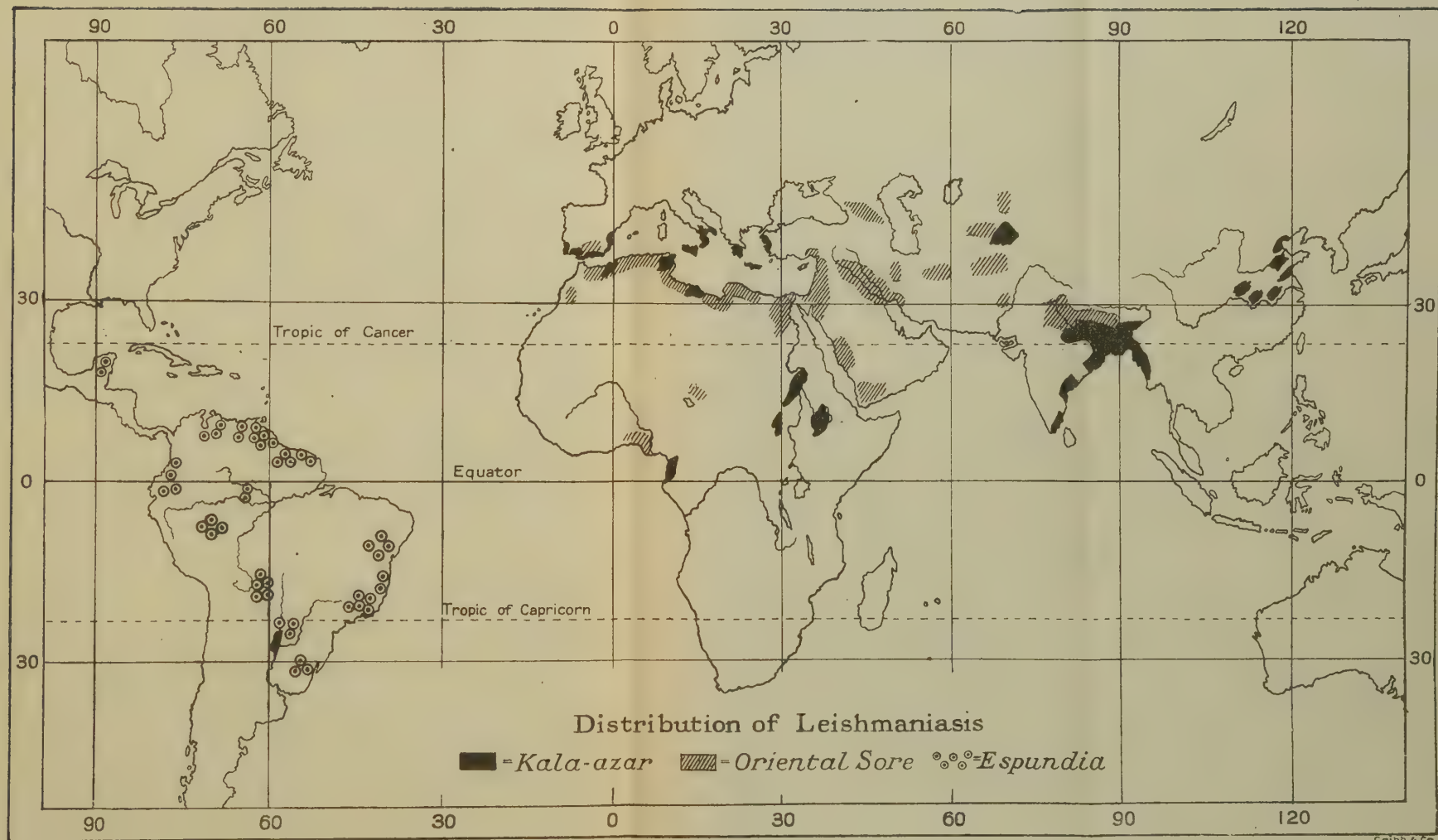
Synonyms.—Tropical Splenomegaly; Black Sickness; Sirkari Disease; Sahib's Disease; Burdwan Fever; Dum-dum Fever; Ponos (Greece).

Definition.—An infective disease characterized by chronicity, irregular fever, enlargement of the spleen and often of the liver, and the presence in these and other organs of *Leishmania donovani*.

History.—The earliest description of this disease is by Clarke (1882), who stated that as far back as 1869 the attention of administrative officers in Assam had been directed to a peculiar disease called by the natives kala-azar, the ravages of which decimated, and in some instances almost depopulated, numerous districts in the Garo Hills.

Owing to the absence of malaria parasites, tertian or quartan periodicity, and the inefficacy of quinine, in the cases of tropical splenomegaly which Manson had studied in England, he came to regard this disease as non-malarial and as one *sui generis*, and suggested in 1903 that it might be a trypanosome disease. In that year Leishman discovered certain small oval bodies in the spleen-pulp of a soldier who had died of "dum-dum" fever at Netley, and surmised these bodies to represent degenerative forms of a trypanosome. Later, Donovan in India corroborated Leishman's discovery. In December, 1903, Manson and Low found similar bodies in the spleen of a patient from India suffering from the same disease, and were able to show that these bodies were not endocorpuseular parasites.

Geographical distribution.—Kala-azar is a widely distributed disease. It occurs in India, especially in Assam, Madras, and along the Ganges and Brahmaputra; in China, north of the Yangtse in a district between the coast and a line joining Peking and Hankow; in the Sudan (Kassala and Blue Nile districts), Western Abyssinia,



MAP III

Tchad territory and northern Kenya ; in French Guinea ; in Tunis, Tripoli, Morocco, Algeria, and (rarely) in Egypt ; in Sicily, Italy, Crete, Spain (in Madrid and the east and south coasts), Portugal. Greece and the Grecian Archipelago (where the disease known as "ponos" has proved to be infantile kala-azar), Malta, and in Russia west and east of the Caspian, in Transcaucasia, and Turkestan. (Map III.) In the New World it occurs to a slight extent in Paraguay and northern Argentina.

Epidemiology.—Our knowledge of the epidemiology of kala-azar is gathered mainly from the Assam epidemic, which began about 1870, when the disease appears to have been introduced from Rangpur. Rogers believed it was originally introduced from Bengal, a theory supported by the names of "Sirkari disease" and "Sahib's disease" given by the Garos, who state that it was unknown among them until after the English took over their country. The epidemic advanced slowly along the valley of the Brahmaputra, taking seven years to spread less than a hundred miles. The introduction of the infection into a village was almost invariably traced to someone coming with the disease on him from an infected locality, though some isolated localities escaped in a remarkable manner. Generally it clung to a place for about six years, and then disappeared without any apparent change in the local conditions. A house seemed to retain the infection for many months; the natives considered that it could not be reoccupied with safety under one year. During the course of the epidemic, kala-azar never extended far above the level of the Brahmaputra valley, the disease appearing first at the foot of the hills, and then spreading between them along the patches of low, flat, terai country. During the years 1922 and 1923 it extended up to the head-waters of that river into the Dibrugarh district, where it had never been known before. At present, kala-azar in India is confined to Assam, Bengal, Bihar and Orissa, and the United Provinces as far as Lucknow, and stretches in a patchy manner down the East Coast as far as Tuticorin. It has never spread to Ceylon. Kala-azar does not occur above an altitude of 4,000 feet.

On account of its deadliness, kala-azar as it swept onwards became a terror to the natives. Those suffering from the disease were turned out of the villages; sometimes they were made unconscious with drink, taken into the jungle and burnt to death. Some villages cut off all communication with neighbouring villages for fear of infection; other villagers deserted their homes and even migrated to a different district.

Napier has pointed out that the distribution of kala-azar in India is associated with one set of physical circumstances—the existence of alluvium and a certain heaviness of rainfall. In Assam there is a very definite house infection which in many cases is traceable to the introduction of a relative from a previously infected house, and there is reason to believe that, when once introduced, kala-azar does not disappear until the whole of the population in the focus has been destroyed.

Although the foregoing are the only recorded examples of kala-azar as a widespread and active epidemic, it had been recognized that a disease clinically identical occurred sporadically in several places in India, the Mediterranean area, the Sudan, and China.

Apparently, then, kala-azar occurs both as a sporadic and as an epidemic disease. In 1904, leishmaniasis was discovered in Tunis by Cathoire, and important studies by the Sergents, Nicolle, and many others have shown that the parasite occurs in many of the islands and countries in the Mediterranean basin; that there it is practically confined to young children—infantile kala-azar—the parasite of which was recognized by Nicolle as a distinct species, *Leishmania infantum*; and, further, that, whilst in India dogs are never affected, in the Mediterranean basin and in Spain, a large proportion of these animals are naturally the subjects of leishmaniasis, and in many cases are closely associated with the similar disease in children.

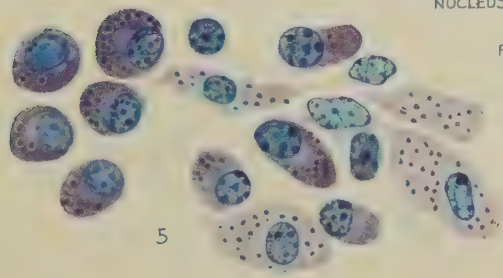
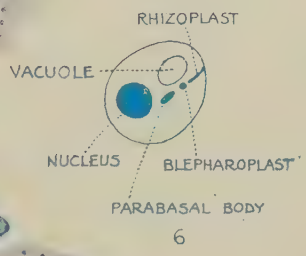
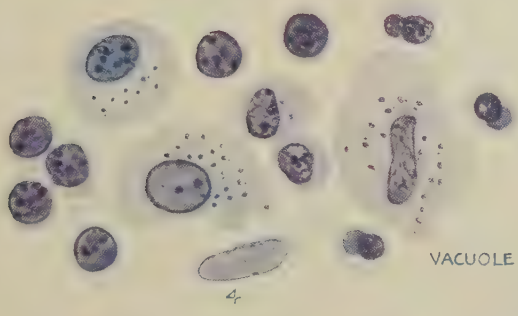
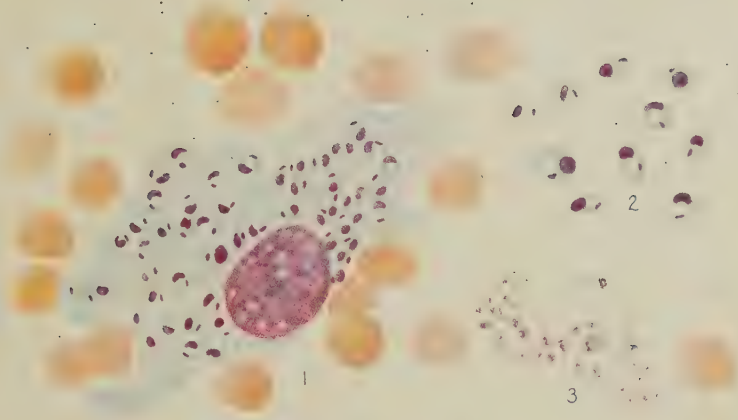
Etiology.—The kala-azar parasite (Plate X) is now generally included by most authorities in the genus *Leishmania*, though some are disposed, on account of its life-history, to regard it as an *Herpetomonas*. We know two stages of this body, intracorporeal and extracorporeal. Possibly these represent respectively asexual and sexual forms; the former found only in man and in some other vertebrates, the latter obtained in artificial culture media and in the sandfly.

The distribution of the parasite within the body of man is very general. Apparently its special habitat is the endothelial cells of blood-vessels and lymphatics. It is particularly abundant in the spleen, in the liver, and in the bone-marrow. (Plate X.)

The Leishman-Donovan body, as it is generally called, is a small ovoid or roundish organism measuring 2–4 μ in diameter. When stained according to Leishman's method it shows two lilac-coloured chromatin masses, one larger than the other, enclosed in a cytoplasm having a faint bluish tint about the periphery. The larger is known as the trophonucleus, the small rod-like body as the rhizoplast. The parasite divides by longitudinal fission.

The parasites, as they occur in man, are probably almost invariably intracellular. They grow and multiply within the host-cell, causing it to enlarge, and then, after disintegration of the nucleus, to disrupt. The parasites so set free either enter other endothelial cells or are taken up by the white blood-corpuscles, in which they are sometimes found in the peripheral circulation. In smear preparations they are often free or in clusters of various numbers, sometimes arranged with great regularity like the merozoites in the segmenting quartan or tertian malaria parasites. Sometimes as many as 50 or 200 parasites, or even more, are found together embedded in a structureless matrix or stroma, probably the remains of the original host-cell.

The parasite can be cultivated outside the body. The medium



J. R. FORD

- 1, Parasites enclosed in endothelial cells in film from spleen puncture, stained with Leishman
- 2, Free forms from spleen.
- 3, Blood-platelets in same film for comparison.
- 4, Parasites enclosed within splenic pulp cells, as seen in section, stained with hæmatoxylin.
- 5, Parasites in plasma and endothelial cells in intestinal mucosa.
- 6, Diagram of Leishman-Donovan body, highly magnified.

LEISHMAN-DONOVAN BODIES IN KALA-AZAR. × 1,000.

used by Rogers was citrated blood. When kept at blood-heat the parasites degenerate and disappear, but at a temperature of 20–22° C. they multiply rapidly and assume an elongated motile flagellated form. The flagellum arises from the rhizoplast and projects at the anterior end of the body as in *Herpetomonas*, but there is no undulating membrane as in the trypanosomes. These flagellated forms measure 12–20 μ in length, and multiply by longitudinal fission. They move actively, flagellum foremost, and tend to agglomerate into rosette groups with their flagella directed centrally. The N.N.N. medium (p. 861) is now considered the best for culture of this organism, but technique must be particularly observed, as bacteriological contamination rapidly kills the parasites. Wenyon has succeeded in keeping the parasite alive in successive subcultures over a period of fifteen years. The flagellated form has not been found in the human body, but Wenyon has noted that these forms may occur associated with typical leishman bodies in canine leishmaniasis. The parasite can be communicated to dogs, cats, jackals, monkeys, rats, voles, hamsters, and mice, provided that large doses of the virus are injected into the peritoneal cavity or into the liver. To infect a dog, it is necessary to inject 2–4 c.c. of a thick emulsion of infected spleen, liver, or bone-marrow. Intravenous injection is by no means so successful, while injections of cultures rarely succeed.

Transmission of the parasite.—It was formerly thought, from the close association of the human and canine disease in the Mediterranean area, that the dog constituted the chief reservoir of infection, but the association is not now so complete as to be conclusive for certain areas, as, for instance, in Persia, where kala-azar in dogs is common, while human kala-azar is absent. In China, a small rodent, the striped hamster (*Cricetulus griseus*), has proved in the laboratory to be extraordinarily susceptible to infection, and this animal has once been found to be naturally infected in the wild state. These are the facts which are known, but they do not at present by any means afford a sure explanation of the peculiar geographical distribution of kala-azar on the grounds that some wild animal is the reservoir of infection to man. On account of the peculiar topographical distribution of kala-azar in India, Sinton first suggested in 1922 that a sandfly (*Phlebotomus*) was the insect vector. A similar suggestion as regards the leishmania of oriental sore had already been put forward by Wenyon in 1911 and subsequently proved correct by the Sergeants in Algiers. Since that time a large amount of work on the subject has been performed by Christophers, Shortt, Knowles, Napier, Barraud,

Lloyd, and Smith, with the result that a very rapid, intensive and remarkable development of *Herpetomonas* forms was found to occur in one species of sandfly—*Phlebotomus argentipes*—when fed on the blood of patients suffering from kala-azar. The whole midgut becomes infected and in some individual insects the infection spreads to the pharynx, and even to the buccal cavity.

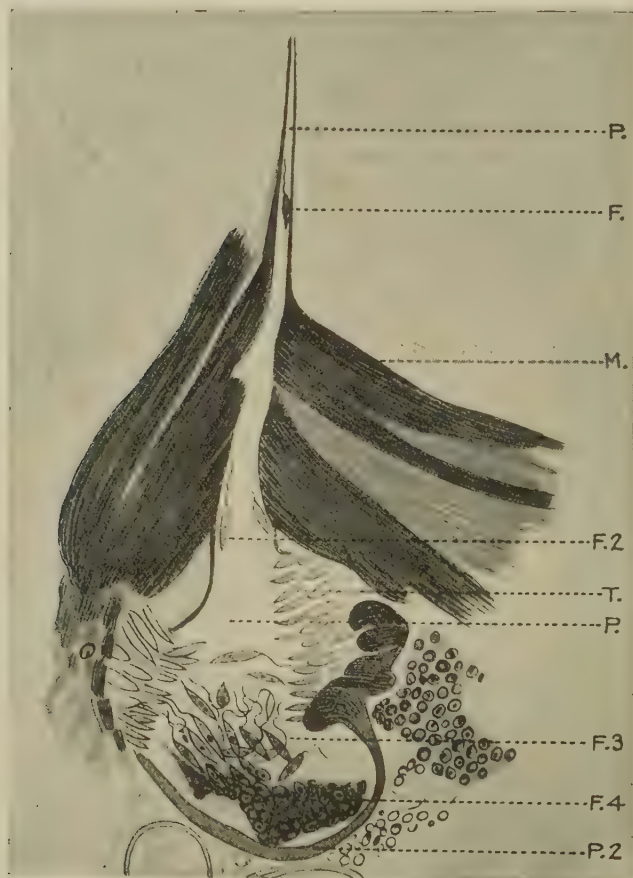


Fig. 35.—Section of *Phlebotomus argentipes*, showing pharyngeal infection with *Leishmania donovani*. (From Indian J. Med. Res.)

P, lumen of pharynx; P2, posterior termination of pharynx; T, ridges of crinkly portion of pharynx; M, muscles of pharynx; F, flagellate near anterior extremity of pharynx; F2, flagellates anterior to crinkly portion; F3, flagellates breaking free from main mass of growth; F4, massive growth of flagellates at posterior end of pharynx.

(Fig. 35.) The distribution of this species of *Phlebotomus* in India, corresponds closely to the distribution of kala-azar; in other endemic areas probably a different species of *Phlebotomus* is involved, as in China, *P. major* and *P. sergenti* (Hindle). One of the main difficulties encountered in these experiments is the delicacy of these small insects and the trouble experienced in keeping them alive longer than five days after feeding. The crucial test, the actual transmission of kala-azar under experimental conditions, still remains to be performed, though hamsters have been infected by injection of crushed sandflies. Probably



Fig. 36.—Chinese hamster (*Cricetulus griseus*). (After Smyly and Young.)

the Chinese hamster and its European congener (*Cricetulus frumentarius*) found to be susceptible to infection (Mayer) will provide the best means of solving this problem. An account of the bionomics of the sandfly will be found on p. 817. Shortt, Barraud and Craighead have reported the occurrence of a naturally-infected sandfly in a kala-azar house.

The hamster (*C. griseus*, Fig. 36) is a small species of the size of a field-mouse, 12 cm. in length and 30 gm. in weight. Common round Peking, it extends into Chinese Mongolia. It makes extensive burrows, frequenting cornfields and destroying quantities of grain. It is greyish-brown in colour, pale beneath, with a decided median dorsal stripe, and has a short, stumpy tail.

Hu and Cash have made the most interesting observation that

the leishman bodies are taken up by the cells of the reticulo-endothelial system, or clasmatocytes, and become massed as a thick layer of heavily infected tissue in experimentally-infected hamsters lying immediately underneath the skin, though externally no change can be seen on the surface of the body. This observation has been confirmed by Hindle (Fig. 37). In skin sections from a fatal case of kala-azar a similar condition was seen. All levels of the skin below the epidermis contained leishmania-filled cells collected in large masses about the sweat-glands and arterioles and scattered diffusely throughout the corium. The relationship

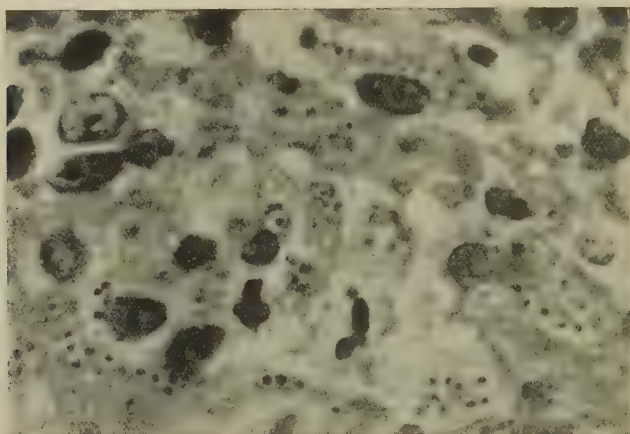


Fig. 37.—Section of subcutaneous tissue of hamster experimentally infected with kala-azar, showing proliferation of clasmocytes containing leishmania in the neighbourhood of blood-capillaries.

(Hindle.)

between this condition and the curious skin eruptions (p. 143) described in India is of interest, and it suggests the possibility of the manner in which the parasites are abstracted by blood-sucking insects when scanty in the peripheral blood.

Formerly it was held, mainly by Patton, that the bed-bug was the most probable insect vector, but investigations by Mackie in 1915 and by Cornwall in 1916 greatly reduced the value of these arguments.

Suggestions have been made that the transmission may be direct from man to man through the fæces. The evidence for this appears to be based upon the fact that leishmania parasites occur in polypoid masses in some intestinal cases, and that leishmania-like bodies have been found in the intestinal mucosa in kala-azar

cases by Mackie, Knowles and others, but a method of transmission so simple as this would eliminate the necessity for the flagellated stage of the organism, which we know must take place. In a certain proportion of advanced cases viable parasites are excreted in the urine.

That kala-azar may occasionally be a congenital infection has been shown by Carmichael Low and Cooke, who proved that the disease developed in a child seven months old, born in England of a mother who suffered severely from kala-azar during pregnancy.

Predisposing causes.—Kala-azar attacks both sexes and all ages, but, unlike malaria, shows a predilection for the acclimatized—the natives; in them it is said to be as severe and fatal as in the case of new-comers. In the Mediterranean basin it occurs almost, though not quite, exclusively in children (five months and upwards); in India it occurs at any age.

Pathology.—The spleen is greatly enlarged, and the thickened capsule may show signs of perisplenitis. The trabeculae are enlarged; the pulp is increased in bulk and full of blood. A section or smear preparation, appropriately stained, will show prodigious growth in the large mononuclear cells. The liver also is generally much enlarged, and is brown or mottled on section. The parasites are in great abundance, occupying large mononuclear cells, attached or free, in the dilated hepatic and portal capillaries throughout the reticulo-endothelial system. Christophers has shown that primarily the parasites are engulfed in macrophage cells of the blood-vessels. There may be some cirrhotic changes, but the hepatic cells, though atrophied and perhaps fatty, never contain parasites. The bone-marrow is similarly packed with parasite-laden cells. Intestinal ulceration is very common, and parasites may be found in the walls of the ulcers, as well as in skin ulcerations and in the lymphatic glands. Occasionally they are found in connexion with the blood-vessels in the kidneys, but never in the epithelium of the secreting tubules. Shortt and others have succeeded in cultivating the parasite from the urine in three cases.

The distribution in the body has been explained by Laveran on the assumption that the parasites are taken up by the endothelial cells, when they multiply till the cell ruptures and the organisms escape into the blood.

Symptoms.—The *incubation period* is difficult to fix. In the case of one Englishman under Manson's care, the time that elapsed from his arrival in perfect health in the endemic region and the onset of the fever which terminated in kala-azar (diag-

When the disease is thoroughly established, emaciation and anæmia become noticeable, and, together with the enlargement of the liver and spleen, cause the patient to present a typical appearance. In China a uniform painless enlargement of the cervical lymph-glands has been observed. Œdema of the legs, sometimes circumscribed œdemas, or even ascites may now be present. In many cases the skin acquires a strange earthy-grey colour; this dusky pigmentation, which has given rise to the native name, *kala-azar*, "the black disease," is best seen on the feet, hands and abdomen in Europeans though very difficult to distinguish in dark-skinned natives. The hair is apt to become dull, dry, and brittle, and may fall out; petechiæ, in the axillæ especially, are not unusual; epistaxis and bleeding from the gums are common. This condition of chronic fever, enlargement of spleen and liver, emaciation, and anæmia (Fig. 38) may continue for months, or even one or two years, until improvement sets in, or more usually—96 per cent. of cases (Rogers), 150 recoveries in 2,000 cases (Price), 24 in 100 cases (Lignos)—until the patient is cut off by an intercurrent disease, especially dysentery (90 per cent.).

The outstanding clinical feature which impresses itself on one's mind is that, in spite of the patient's weak and emaciated condition, the pyrexia, and the protuberant abdomen due to splenic enlargement, he preserves a good appetite and a clean tongue, while with a temperature of 102° F. he may be doing his work and be quite unaware that he has fever. In this respect *kala-azar* differs from malaria and other toxic fevers, such as typhoid.

The number of red corpuscles is not infrequently over 4,000,000, and, as a rule, over 2,500,000 even in advanced cases.

The most remarkable change seen in the blood is the great and constant reduction in the number of leucocytes. Instead of there



Fig. 38.—*Kala-azar* in Indian coolie boy, showing characteristic abdomen and great emaciation. (Colonel F. P. Mackie, I.M.S.)

being 1 white to about 625 red, as in a normal subject, the proportion is commonly from 1:2,000 to 1:4,000, and may be lower still. The reduction is most marked in the polymorphonuclear variety; the lymphocytes and large mononuclear leucocytes, although greatly reduced in number, usually show a relatively increased percentage, as in some other protozoal diseases. The blood-pressure is generally low, the systolic reading being below 100 mm. of mercury. Hæmic murmurs of the heart are noted. Hæmorrhages may occur from any part of the body, and purpuric patches may appear on the skin after local injury. Death may ensue from several causes. When due to the disease alone it results from exhaustion. Dysenteric symptoms are frequent, and may be due to intestinal lesions caused by Leishman-Donovan bodies, or to a superadded infection with amœbic or bacillary dysentery. Broncho-pneumonia and cancrum oris are frequent terminal symptoms. Proctor, however, reports that the latter complication can be arrested in the early stages by scrupulous daily inspection of the mouth. Should a grey line of ulceration on the gums be seen, it should be energetically treated with carbolic acid and spirit.

Dermal leishmanoid.—A cutaneous form of leishmaniasis, in which the parasites occur in nodules of the skin, was apparently first reported by Thomson and Balfour in the Sudan in 1909. It was recognized by Bramachari in India and described under the name of dermal leishmanoid, but now Acton and Napier describe the same condition as post-kala-azar leishmaniasis. It is certainly a sequel to generalized infection with *L. donovani*. More than half the patients who exhibit this curious eruption have suffered from kala-azar about one year previously, and have received antimony treatment for this disease. The *Leishmania* are found in smears from the nodules, and cultures have been obtained from the lesions. It is not at all clear at present what the significance of this phenomenon is, or what factor causes the organisms to establish themselves in the skin.

The first or depigmented stage usually appears as depigmented patches on the face and upper extremities, gradually spreading to the remainder of the body. Minute dots gradually enlarge till they become irregular areas half-an-inch in diameter. The second, or nodular stage, is seen about two years after kala-azar treatment. Usually the nodules replace the depigmented patches, but there are certain areas, such as the face, where the nodules appear much earlier than in other parts of the body. The nodular lesions may extend to the mucous membranes and may closely resemble

leprosy. There is an xanthomatous form, known as *Xanthoma tuberosum multiplex*, which is quite unmistakable, and in which the parasites have been observed in the peripheral blood (Fig. 39).



Fig. 39.—Dermal leishmanoid. Extensive nodular lesions on face; this condition resisted all forms of treatment. (*Acton and Napier, Ind. Jl. Med. Res.*)

The only drug which has any beneficial effect is antimony, but some cases are entirely resistant to it.

Diagnosis of kala-azar.—Irregular chronic fever with enlargement of the spleen and a diminution in the number of leucocytes in patients from the endemic zone suggests kala-azar. An examination of the blood can at once exclude leucocythæmia and, if taken together with absence of tertian or quartan periodicity and the inefficacy of quinine, malaria. Differential diagnosis from typhoid and malignant endocarditis should present no special difficulties. Trypanosomiasis and kala-azar may be difficult to distinguish between, and unless their respective parasites are detected a positive diagnosis is impossible, although geographical considerations, the rash, and lymphatic enlargements may assist.

Splenic puncture must not be lightly undertaken. A preliminary examination of the blood should always be made, not only with a view to ascertaining the presence of the leishman body, but to exclude leucocythæmia and obviate the necessity for splenic puncture, and the attendant risk of fatal hæmorrhage so easily induced in that disease. When the liver is enlarged, it should be selected, as a less vascular organ and less easily torn, for puncture, but, as a general rule, the parasites are not so abundant in this organ as in the spleen. In performing puncture, the abdomen had better be fixed firmly with a binder to prevent, as far as possible, movement of the diaphragm and consequent risk of tearing the punctured organ. The patient should be injected with $\frac{1}{100}$ gr. of atropine one hour previously, and the puncture site infiltrated with novocain to deaden pain. The administration of 30 gr. of calcium lactate the evening before and on the morning of the puncture, and the fixation of the lower border of the spleen are advocated. A hypodermic needle, scrupulously clean and dry,¹ and connected with the barrel of the syringe by a short length of rubber tubing, should be used, the patient being directed not to start or breathe when the puncture is being made. The type of needle is most important. The bore should be neither too big nor too small. The Editor has found Maw's size No. 10, with a shaft 40 mm. in length, the most suitable. Failure to draw blood is not to be regarded as failure to obtain material for microscopical examination; on the contrary, it is an advantage, as the object is to procure spleen or liver pulp, not blood. After the contents of the needle have been blown out on a slide, it may be transilluminated by an electric pocket-torch to discover the minute sago-like masses of splenic tissue. A film should then be spread and, after it has dried, stained by Leishman's or Giemsa's method, and then

¹ The presence of a trace of water in the needle will distort or burst the parasite and render it unrecognizable.

examined with a $\frac{1}{12}$ in. objective. The parasite is easily recognized by its size, shape, and two chromatin masses. The recent discovery of leishman bodies in the subcutaneous tissues suggests that removal of a piece of skin may be a safe and rapid method of forming a diagnosis.

Diagnosis can be made by abstraction of red bone-marrow and demonstration therein of the Leishman-Donovan body. The epiphysis of the tibia in small children is suitable, and the sternum in adults.

The frequency with which this parasite appears in the blood has been a matter of much discussion. Undoubtedly, in some places, as in Madras and Assam, it occurs in about 20 per cent. of all cases examined, and therefore the diagnosis may be made by simple blood examination; but this is by no means the case in other parts of the world.

Knowles and Das Gupta employ thick films prepared by placing four drops of blood on a clean slide, mixed so as to cover an area of $\frac{1}{4}$ sq. in. The film is covered with a Petri dish, dried at 37°C. for two hours. It is then flooded with glacial acetic acid (2.5-per-cent.) 4 parts, crystalline tartaric acid (2-per-cent.) 1 part. The action should be complete in five to ten minutes. After tilting off the fluid, the film should be fixed with methyl alcohol and stained with dilute Giemsa. By this method the parasites may be found enclosed in leucocytes, in 67 per cent. of kala-azar cases.

A less elaborate technique is employed by Shortt and his colleagues. A small drop of blood is placed at one end of a slide and a second one applied in the usual manner and pushed till the blood is almost exhausted. At this point it is abruptly lifted off, with the result that the blood-smear ends in a straight edge which is somewhat thicker than the rest of the smear, and in this the parasites can be demonstrated within the leucocytes.

By centrifuging 5 c.c. of blood diluted in Locke's solution (sodium chloride 9.2 gm., potassium chloride 0.5 gm., calcium chloride 0.1 gm., sodium citrate 10 gm., distilled water 1,000 c.c.), at a speed of 750 revolutions, Young and van Sant state that parasites are readily discovered in films made from the bottom of the centrifuge-tube. It is stated that the parasites appear in the blood-stream after injection of 10-20 min. of a 1:1,000 solution of adrenalin. According to Wenyon and others, the presence of the parasite in the peripheral blood can best be demonstrated by blood-culture. For this purpose 2 c.c. of blood should be drawn off by means of a 2-c.c. Record syringe and mixed with 1 c.c. of 6-per-cent. citrate solution in a sterile tube, which should be placed in a cool incubator and allowed to sediment for two hours. The deposit at the bottom of the citrate solution is then drawn up by means of a pipette, inoculated into two or more tubes of N.N.N. medium, and again placed in a

cool incubator. Examination of the cultures should be made about the tenth day, when flagellate forms may be observed, but it is not wise to discard the tube as negative until at least twenty days of incubation have elapsed. Spleen pulp may also be cultured in the same manner.

Biochemical reactions.—There appears to be little evidence for the statement that the serum of kala-azar cases gives a positive Wassermann reaction. The alkalinity of the blood is said to be decreased, while in some cases the coagulation-time is very considerably prolonged.

Aldehyde test (or the serum-formalin reaction) (*Napier*).—This test has proved to be very useful as a method of diagnosing kala-azar on a large scale among gangs of coolies where systematic splenic puncture is obviously impracticable. For this purpose about 5 c.c. of blood is withdrawn from a vein and allowed to stand a sufficient time for the serum to separate; 1 c.c. of clear serum is then placed in a test-tube (3 by $\frac{1}{2}$ in.), and to this 1 drop of 30-per-cent. formaldehyde, or commercial formalin, is added. The serum is at once well shaken and placed in a test-tube rack at room-temperature. In a certain proportion of cases of kala-azar, solidification of the serum takes place within a space of three minutes, but a control of normal serum should always be made. Napier himself states that “jellification” with opacity (like the white of an egg) of the serum may be taken as diagnostic of kala-azar if the disease is of three or four months standing, but milkiness of the serum without solidification only takes place in early cases of the infection. Should the serum be hæmoglobin-stained, this will change to chocolate-brown after twenty-four hours. In certain cases of syphilis, leprosy, phthisis, and malaria the serum will solidify, but remains clear and does not become opalescent as in kala-azar.

In kala-azar it has been proved that the plasma globulins are increased, while the albumins are diminished. In kala-azar, the albumins are 2·8; the globulins 4·0, as compared to 4·5 and 2·0 per cent. respectively in the normal. Auto-agglutination of the red blood-corpuscles is often noted as in trypanosomiasis, more especially in advanced cases.

Chopra has pointed out, and Napier has confirmed, the curious fact that the addition of a 4-per-cent. solution of pentavalent antimony compounds to kala-azar serum causes a heavy precipitate, the amount of which corresponds to the efficacy of that compound in the treatment of the disease.

In the Chinese form of the disease, in which enlargement of the lymphatic glands occurs, diagnosis may be made by gland puncture or excision.

The **differential diagnosis** has to be made from that of splenic anæmia, Banti's disease, and Egyptian splenomegaly, which, save for the absence of the parasite and the characteristic pyrexia, may closely simulate kala-azar. Visceral syphilis with enlargement of liver and spleen may have to be excluded. The same may be said of malignant disease and tuberculosis of the spleen. In China and Japan kala-azar may have to be differentiated from intestinal

schistosomiasis, in which enlargement of the abdominal organs may occur. The remarkably clean tongue and the good appetite serve in some measure to differentiate kala-azar from chronic malaria, to which may be added the considerable emaciation, the absence of extreme anæmia, the double daily rise of temperature (in 88 per cent. of cases), distension of the superficial abdominal veins, and pigmentation of the extremities.

Treatment.—Intravenous *antimony tartrate* (sodium-antimony-tartrate),¹ first introduced by Vianna in Brazil for dermal leishmaniasis, has been attended by remarkable results in kala-azar. If instituted before the case has become hopeless, it seldom fails to ensure recovery.

For routine use in India, tartar emetic is usually made up in a 2-per-cent. solution, the initial dose being $\frac{1}{2}$ gr. increasing gradually to a maximum individual dose of $1\frac{3}{4}$ gr. (5·8 c.c. of the solution). As a general rule, Europeans can tolerate larger doses than the Indian; in the former the maximum individual dose is $2\frac{1}{2}$ gr. An injection may be given every third day for two to three months. In children and in elderly patients the initial dose must be considerably smaller than that for those in more robust health, and should not exceed $\frac{1}{3}$ c.c. (of the 2-per-cent. solution) per 10 lb. of body-weight. Therefore, for children under six years of age, 1 c.c. of the solution should be given for the first dose, and increased by $\frac{1}{2}$ c.c. up to a maximum of 3 c.c. The difficulty of finding suitable veins for intravenous injection in small children may be overcome by injecting the drug in a dose of 12 mg. ($\frac{1}{5}$ gr.) in 60 c.c. of saline *intraperitoneally* in the middle-line of the abdomen just below the umbilicus. Three injections weekly can be given to a child of six months till a total of 4 gr. has been absorbed. In routine treatment of kala-azar in Assam, McCombie Young gives 30 gr. of tartar emetic over a period of three months. Bi-weekly injections are given with tabloids of the drug, which are dissolved in water so as to make 100 c.c. of a 1-per-cent. solution, of which 6 c.c. contain approximately 1 gr. The working rule adopted is that, should the pyrexia persist after two weeks, the treatment should be continued for two months; if pyrexia persists for three weeks, treatment should be extended to three months; and so on. According to Napier, the maximum dose of sodium- or potassium-antimony-tartrate to effect a cure, in any but a resistant case, is 60 gr. per 100 lb. of the patient's body-weight. The effects of antimony tartrate vary much in different patients, as the disease is not equally amenable to treatment at all stages. In hospital practice in England, and in treating individual cases, it is advisable not to use standardized solutions such as those referred to above, as there is reason to believe that they deteriorate or decompose on keeping (*see* p. 666); a fresh solution should be made up at each injection. The initial dose should be $\frac{1}{2}$ gr. in 5 c.c. of distilled water (the use of saline is unnecessary). The dosage should be increased by $\frac{1}{4}$ gr. at each injection until the maximum of $2\frac{1}{2}$ gr. is reached; from 1 gr. upwards the solution should be made in 10 c.c. of distilled water (*see* p. 520). The addition of 5-per-cent. glucose to the solution has the remarkable effect of neutralizing or minimizing the toxic effects. It is

¹ Potassium-antimony-tartrate has a similar action, but is less commonly employed.

advisable to give the injections slowly—as a working rule, at the rate of 1 c.c. in 8 seconds. The injection should not be given within two hours of a meal. Great caution should be exercised in the case of patients showing cardiac irregularity and in those with albuminuria. Within a few minutes of the injection the toxic symptoms of tartar emetic are often noted; these consist of coughing, a feeling of constriction in the chest, and sometimes nausea and vomiting, but are less commonly observed when a small amount of fluid is used as the menstruum. That a cure is being effected may be inferred from the absence of fever, a steady gain in weight, and diminution in the size of the spleen. In small children tartar emetic can be successfully injected into the jugular vein, the head being allowed to hang over a table in order to make the vein prominent.

Intramuscular injection of antimony tartrate produces some local reaction culminating in necrosis and abscess-formation. The practice has therefore been abandoned.

The particular manner in which antimony acts upon the Leishman-Donovan body is still undecided, for it is known that this parasite may still be cultured from splenic puncture, even when the case is progressing favourably under treatment, with consequent shrinkage of the spleen.

Antimony tartrate as a routine treatment for kala-azar is now being rapidly superseded by more highly organized pentavalent compounds of antimony originally prepared by the firm of Von Heyden. The first of these preparations—stibacetin (acetyl-p-aminophenyl stibiate of sodium)—when injected in doses varying from 0.01 gm. ($1\frac{1}{2}$ gr.) to 0.3 gm. ($4\frac{1}{2}$ gr.) gave good results and can be tolerated as an intramuscular injection. This was a distinct advance, as the intramuscular method has been applied in Italy to the treatment of kala-azar in children to whom the intravenous method was not applicable.

Of the various organic compounds now in use, *stibosan* (meta-chlor-para-acetylaminophenyl stibiate of sodium) is the most universally commended and is known as Von Heyden 471. In India it has been well reported on by Napier, while results of treatment in individual cases in England and elsewhere have been satisfactory. The customary and usual initial dose is 0.1 gm. ($1\frac{1}{2}$ gr.), but for robust individuals it may be as high as 0.2 gm. (3 gr.). The drug is obtainable in sealed ampoules containing 0.2–0.3 gm. each. The contents (a flocculent powder) are dissolved in a small quantity of freshly-distilled sterile water and can be given in a 5-per-cent. solution. Thus for 0.05 gm., 1 c.c. of fluid will be required; for 0.1 gm. 2 c.c., and so on. For general use, however, it is safe to dissolve the drug in 10 c.c. of distilled water. The maximum individual dosage for an average individual is 0.3 gm. ($4\frac{1}{2}$ gr.); in resistant cases 0.6 gm. (9 gr.) may be tolerated and often successful where smaller doses fail. In weak patients the initial dose should be 0.05 gm. ($\frac{3}{4}$ gr.), the maximum, 0.25 gm.

(3 $\frac{3}{4}$ gr.). The injections may be given twice or three times weekly, and the number required to effect a cure will vary from 11 to 15. The requisite amount of stibosan is about 3 grm. for an adult weighing 100 lb., or about 5 grm. for an average European. Exceptionally, 15 or more grm. may be required. Children tolerate relatively large doses of the drug. At three years of age the maximum dose is 0.1 grm.; at nine years 0.2 grm., and from twelve onwards 0.25 grm. In children between one and two years of age *intramuscular* injections up to 0.1 grm. can be given without causing more than slight local pain. The presence of ascites is a contraindication to the use of the drug, but pulmonary complications, albuminuria and diarrhoea are not. Should jaundice occur, the injections should be discontinued. The advantage of stibosan is the diminished toxicity and rapidity of action as compared with tartar emetic. Severe reactions, fever, cough and vomiting are not usually encountered. The drug is stable and does not change in contact with air. For hospital use the drug is supplied in bottles of 10 grm.

Other compounds of importance are *stibamine-glucoside* (neostam) and *urea stibamine*. The dosage and number of injections are the same as already detailed for stibosan. The reports on neostam are as satisfactory. Urea stibamine (Bramachari) appears to be a compound of urea with stibamine (p-aminophenylstibinic acid) and is apt to undergo chemical change if kept in contact with air. It has been favourably reported upon in Assam and from sources in India. The total amount required to effect a cure is from 2 $\frac{1}{2}$ –3 $\frac{1}{2}$ grm., and urea stibamine can be given in a much more exhaustive dosage so that treatment can be shortened from three months to one; eleven injections are generally necessary. If, for some reason or other, intermission in treatment takes place, the parasites become antimony-fast. In 1925–1926, out of a total of 60,940 patients treated with the drug in Assam, 24,700 were discharged cured.

Urea stibamine may be given intramuscularly to infants in doses of from 0.01–0.08 grm. in 1–2 c.c. of distilled water, a total of 0.65 grm. being necessary.

The recent reports of Napier show that the series of pentavalent compounds of antimony is by no means exhausted. *Von Heyden 693* (the amino salt of para-aminophenylstibinic acid) contains 40 per cent. of metallic antimony, with low toxicity. The initial dose for an adult is 0.1 grm.; the second 0.2 grm.; the third 0.3 grm. This compound appears to be especially well tolerated. About ten injections are required for an average case, and a total

of 2·7 grm. is necessary to effect a cure. Vomiting in some cases is the only toxic symptom noted.

As a means of stimulating a leucocytosis and aiding drug treatment, Muir injects 0·5 c.c., at frequent intervals, of a mixture composed of turpentine, 1 dr., creosote, 1 dr., camphor, 1 dr., olive oil, 2½ dr.

Finally, as adjuvants to treatment, the expulsion of intestinal parasites, the treatment of coincident malaria with quinine, change to a healthy climate, good food, warmth, rest, physical comfort, and good hygienic conditions are indicated. Even in a case reacting favourably to treatment parasites may still be found by spleen puncture.

Prophylaxis.—Having regard to the character of the disease, in the endemic districts the cases should be dealt with as infectious; they should be isolated, and the houses and fomites should be disinfected or burnt. Domestic and personal cleanliness is of great importance. Infected dogs should be destroyed; in fact, in the endemic districts dogs should be kept away from association with man. By segregation of the sick, burning of houses, clothing, and furniture, etc., and provision of new huts, Price, Rogers, and Young have succeeded in exterminating the disease in infected coolie lines. Good results in prophylaxis have already followed the actual treatment of cases on a large scale. Should the sandfly prove to be the true vector, then energetic measures against that insect will have to be instigated (see p. 213).

Relationship of infantile to canine kala-azar.—Some authorities consider the form of kala-azar which occurs in the Mediterranean area to be a distinct variety, mainly on its supposed predilection for children and its association with a similar disease in dogs. Nicolle has differentiated the parasite, which is morphologically indistinguishable from *L. donovani*, as *Leishmania infantum*; in fact, Brumpt considers that this type is normally a parasite of the dog, and that it only attacks children accidentally. According to recent work by Hindle, Chinese hamsters inoculated with cultures of *L. infantum* exhibit a peri-arthritis of the limbs which is not induced by other species of leishmania.

In the Mediterranean area adults are not immune to infection, while in India children are more frequently attacked than was at first supposed. The close association of the canine and human disease in the Mediterranean area is far from being always observed: thus, dogs are commonly found infected in Morocco, while only recently has a single human case been seen there; and the same

obtains in Marseilles. The canine disease also occurs in Dakar and in Teheran, where kala-azar is unknown.

The rate of infection of dogs with *Leishmania* is as follows: Tunis, 1·8 per cent.; Algiers, 7·1 per cent.; Lisbon, 3·7 per cent.; Athens, 13·75 per cent.; Malta, 14 per cent.; Rome, 16 per cent.; Messina, 81 per cent.; Island of Hydra, 17 per cent. The disease occurs in dogs at any age, and the parasites, indistinguishable morphologically and culturally from *L. donovani*, are found in large numbers in bone-marrow, spleen, and liver.

In dogs the disease produces a subacute or chronic disease characterized by emaciation, anæmia, muscular atrophy, tremors and pareses. Spleen and liver may be greatly enlarged, and the hypertrophy detectable during life. Certain forms may resemble rabies.

Relationship of kala-azar to oriental sore.—Manson suggested that the relationship between oriental sore and kala-azar might be compared to that of vaccinia and variola. He based his view upon the immunity produced by one attack of oriental sore against further infections of the same disease; and upon the well-recognized dissimilarity in the distribution of these two diseases, for in India, where kala-azar is common, oriental sore is rare, and vice versa. If the parasite of kala-azar is identical with that of oriental sore (*Leishmania tropica*), then the parasite must in some way have been deprived of its virulence; for whereas kala-azar is often a fatal disease, oriental sore is eminently benign. In view of these facts, Manson suggested that inoculation with cultures of *L. tropica* might confer a protection against subsequent infection with kala-azar, and that this method might be used as a prophylactic.

The suggestion has to a certain degree proved true, for Nicolle has succeeded in producing some amount of immunity to generalized leishmaniasis in dogs and monkeys by injecting them intraperitoneally with cultures of *L. tropica*.

II. ORIENTAL SORE

Synonyms.—Tropical Sore; Bouton d'Orient; Delhi Boil; Cutaneous Leishmaniasis; Bouton de Biskra; Bouton de Bagdad; Aleppo Boil; Salek (Persia), etc.

Definition.—A specific ulcerating granuloma of the skin, endemic within certain limited areas in many warm countries. It is caused by a species of *Leishmania*, and is characterized by an initial papule which, after scaling and crusting over, generally breaks down into a slowly extending and very indolent ulcer. Healing after many months, it leaves a depressed scar. The sore is inoculable and, usually, protective against recurrence.

History.—In 1885 Cunningham first described certain deeply staining parasitic bodies in mononuclear cells derived from these sores; J. H. Wright in 1903 renamed them *Helcosoma tropicum*. The observation has been abundantly confirmed, and the parasite is regarded as identical with the Leishman-Donovan body, and is known as *Leishmania tropica*.

Geographical and seasonal distribution.—Morocco, the Sahara (Biskra, Gafsa), Egypt, Crete, Cyprus, Sicily, Asia Minor, Syria (Aleppo), Palestine (Jericho), the Sudan, Nigeria, Mesopotamia (Bagdad), Arabia, Persia, the Caucasus, Turkestan, India (Lahore, Multan, Delhi, Dera-Ismail-Khan, etc.). In South and Central America it is often, but not invariably, found in association with naso-pharyngeal leishmaniasis, especially in Peru, Bolivia, Brazil, the Guianas, and Mexico. (Map III.) Recently it has been reported from North Queensland.

In the tropics this form of ulceration is especially prevalent about the commencement of the cool season; in more temperate climates, towards the end of summer or beginning of autumn. Years of prevalence may be succeeded by years of comparative rarity—possibly in harmony with altered sanitary conditions. In Delhi, for example, in 1864, from 40 to 70 per cent. of the resident Europeans were affected with the local sore; on certain sanitary improvements being effected, the frequency of the disease was immediately materially reduced.

Epidemiology and endemiology.—Although oriental sore may occur in countries where kala-azar is endemic, its distribution is as a rule quite distinct (*see* Map III). It has been pointed out that in India cutaneous leishmaniasis is confined to the west, whereas kala-azar is endemic on the east coast. In North Africa oriental sore occurs north of latitude 35°, whereas kala-azar is found south of this line. In Persia and Mesopotamia, where oriental sore is very common, cases of kala-azar are absent.

In the endemic areas, oriental sore appears to have a seasonal preference, making its appearance between September and January; in cities like Aleppo and Bagdad, where the disease is very common, children usually acquire it between 2 and 3 years of age, and it appears to be quite exceptional for any native to attain maturity without having had one or more of these sores. In fact, it may be said that every woman in Bagdad bears on her face marks of the ravages of this disease.

Oriental sore occurs as a natural disease in dogs. The organism has been demonstrated in cutaneous sores on the ears, lips, nose and inner canthus of the eye of these animals in Teheran, Tashkent, Mesopotamia (where it is only seen during the winter months), and recently in South America and India. Oriental sore has been found as a natural infection of the brown bear in Turkestan. An allied form (*L. myoxi*) occurs in the dormouse.

Etiology.—Section of the papule displays an infiltration of the derma by a mass of small round granulation cells. These lie

between the normal elements of the tissue, particularly about blood-vessels, lymphatics, and sweat-glands; towards the centre of the lesion they completely replace the normal structures. The parasites are found in the granulation tissue at the edge of the lesion, and may be demonstrated in scrapings; care must be taken to avoid obtaining too much blood. The parasites sometimes occur in rosettes or aggregated masses of as many as a hundred individuals and are often enclosed in macrophage cells or in leucocytes; giant cells are frequently found in the deeper layers.

The cultivation of the parasite, first carried out by Nicolle, is easily effected in the N.N.N. medium in the same manner as is kala-azar. The surface of a non-ulcerating sore is first painted with iodine and then punctured with a fine glass pipette, in order to collect material for inoculation. The parasites, as in the case of *L. donovani*, grow best in the condensation water. In heavy infections, flagellates appear in forty-eight hours, but in scanty ones, not for three weeks or more.

The parasites undergo the same changes in culture as do *L. donovani*, but it has been remarked that they are able to flourish in conjunction with contaminating micrococci which the parasites of kala-azar are unable to do. Noguchi has shown that the addition of immune serum from an experimentally-inoculated rabbit causes the organism to grow in clumps.

Epidemiological considerations suggest that the infection is disseminated by the agency of some small biting fly. Wenyon, in 1911, first suggested the sandfly (*Phlebotomus*) as the possible vector in Bagdad, and he found that 6 per cent. of these insects caught in Aleppo had a flagellate of the *Leptomonas* type in their intestinal canals—an observation which has been confirmed in India and elsewhere. Recently, more definite evidence has been brought forward by the Sergents, Parrot, Donatien and Béguet (1921), who have described the production of an oriental sore on the arm of a man in Algiers two-and-a-half months after the scarified skin had been treated with a saline suspension of crushed *Phlebotomus papatasi* which had been collected three or four days previously. The convincing part of this experiment is that the sandflies were caught in Biskra, an oasis where oriental sore is very common, and transported 600 kilometres to Algiers, where the disease does not occur. Of the great number originally caught, only seven remained alive, and these were used for the experiment.

Recently these experiments have been successfully repeated by Adler and Theodor in Palestine with a *Herpetomonas* found as a natural infection in the same species of sandfly.

Monkeys and dogs have proved to be experimentally inoculable, while donkeys, horses, goats, and sheep are refractory.

As a rule, second attacks do not occur. Observing this, the Jews of Bagdad at one time practised on their young children oriental-sore inoculation.

Neither race, nor sex, nor age, nor occupation, nor social condition materially influences susceptibility.

Incubation period and constitutional symptoms.—The incubation period of oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable oriental sore which did not appear until five months after the patient had been exposed to any possibility of infection. Wenyon inoculated himself with oriental sore in Aleppo; it was not until six-and-a-half months later that a leishmania-containing papule, subsequently developing into a sore, appeared at the site of inoculation. In other cases the incubation period has been as much as fifteen months, or even longer.

Symptoms.—The local lesion in oriental sore commences as a minute itching papule which tends to expand somewhat as a shotty, congested infiltration of the derma. After a few days or weeks the surface of the papule becomes covered with fine, papery scales. At first these scales are dry and white; later they are moister, thicker, browner, and adherent. In this way a crust is formed which, on falling off, or on being scratched off, uncovers a shallow ulcer (Fig. 40). The sore now slowly extends, discharging a scanty ichorous material; this from time to time may become inspissated, and a crust forms, while the sore continues to spread underneath. The ulcer extends by the erosion of its perpendicular, sharp-cut, and jagged edge, which is surrounded by an areola of congestion. Subsidiary sores may arise around the parent ulcer, into which they ultimately merge. These sores, usually about an inch in diameter, may come, in some instances, to occupy an area several inches across.

After a variable period, ranging from two or three to twelve or even more months, healing sets in. Granulation is slow and frequently interrupted. Often it commences at the centre while the ulcer may be still extending at the edge; often it is effected under a crust. Ultimately a depressed white or pinkish cicatrix is formed. Contraction of the scar may cause considerable and unsightly deformity.

Oriental sore may be single or multiple. Two or three sores are not uncommon ; in rare instances as many as one-hundred-and-fifty have been counted on the same patient. They are mostly situated on uncovered parts—hands, feet, arms, legs, and, especially in young children, on the face ; rarely on the trunk ; never on the



Fig. 40.—Oriental sore. (After Wenyon. Photo: R. McKay, reproduced in "*Journ. Lond. School Trop. Med.*")

palms, soles, or hairy scalp. Occasionally these ulcers may occur on the ears.

In a very few instances the initial papule does not proceed to ulceration, but persists as a scaling or scabbing, non-ulcerating, flattened plaque—just as sometimes happens in the case of the primary sore of syphilis. Sometimes the ulcer is quite superficial, an erosion rather than an ulcer. Occasionally, from contamination with the virus of some other infectious acute inflammatory skin

disease, the primary lesion may become complicated, and perhaps a source of serious danger. Otherwise, oriental sore is troublesome and unsightly rather than painful or dangerous.

Verrucose form.—A peculiar kind of dermal leishmaniasis has been described by Ferguson and Richards as occurring in Egypt, under the name of parasitic granuloma (Figs. 41, 42). These lesions, which usually affect the lower extremities, resemble warty out-growths or papules; they may be solitary or multiple, and may be the result of auto-inoculation. They are best treated by excision.

Lupus-like lesions.—Christopherson has described discrete lupus-like nodules occurring on the cheek, in general appearance resembling lupus vulgaris, but containing Leishman-Donovan bodies. A cheloid form has also been described.

Generalized non-ulcerating form (dermal leishmanoid).—Bramachari has described papillomatous nodules occurring over the whole of the body, due to Leishman-Donovan bodies. At first they were thought to be tubercular leprosy. Four cases have been observed in India, all of whom had been treated previously for kala-azar and had apparently recovered after antimony injections. It was originally suggested that these skin lesions are caused by *L. donovani* which has been modified by antimony treatment, but this view is by no means established as correct. Provisionally, this form is here described as separate from kala-azar. Christophers, in 1904, gave an account of similar papular lesions occurring on the thighs and scrotum, arms and neck, in undoubted cases of kala-azar. (See p. 143.)

Diagnosis.—On clinical grounds these sores have to be distinguished from the desert or veld sore (p. 627), tertiary syphilis, ulcus tropicum, and blastomycosis. The distribution of the sores and the presence of the Leishman-Donovan body render the diagnosis a matter of no very great difficulty. The parasites are best demonstrated by sterilizing the skin at the edge of the ulcer, and running in a fine glass pipette through a puncture made in the skin, with the object of getting beneath the ulcer so as to obtain serum and tissue cells—but not blood—if possible, free from bacterial contamination. This is a much better method than scraping the surface of the ulcer with a blunt needle or with a fine knife. The cultural method may also be employed. Care must be taken to distinguish the Leishman-Donovan bodies from yeasts which are sometimes present in cutaneous ulcers and may simulate them.

Treatment.—The disease tends to disappear spontaneously on removal from the endemic area, in about one year. The best treat-

ment is the *intravenous injection of tartar emetic*, or sodium-antimony-tartrate, in 2-4-per-cent. solution, as already described for kala-azar. This should be done whenever feasible, beginning with

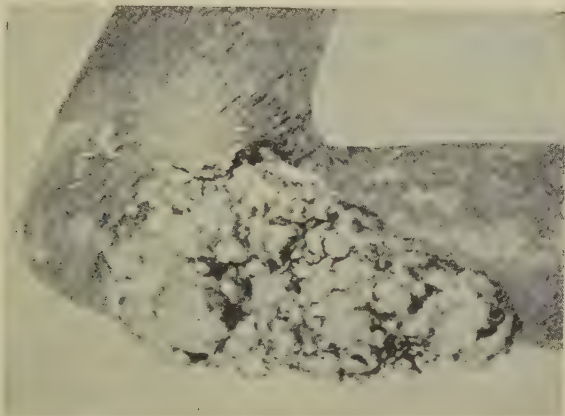


Fig. 41.—Diffuse cutaneous leishmaniasis of the arm in an Egyptian.
(*Ferguson and Richards* By permission of *Liverpool School of Trop. Med*)



Fig. 42.—Diffuse cutaneous leishmaniasis of the leg in an Egyptian.
(*Ferguson and Richards*. By permission of *Liverpool School of Trop. Med.*)

$\frac{1}{2}$ -gr. doses. As solutions of antimony do not keep well, they should be freshly made up each time. Limiting the amount of menstruum prevents severe reactions from arising, so that this treatment may be employed in the out-patient department. Injections should be given every third day, and as a rule 10–15 gr. of antimony tartrate are sufficient to effect a cure. This method, however, is not invariably successful. The employment of other antimony compounds such as stibacetin and stibosan (*see* p. 148) has given equally good results in a shorter period.

Treatment by tartar-emetiic ointment.—Successful results have been obtained with tartar-emetiic ointment. It should be made up in a strength of 1–2 per cent. in the B.P. paraffin ointment. It is apt to be very irritating to the unbroken skin, and some people cannot stand this strength. The ointment is best smeared on the sores at night and allowed to soak in. The addition of cocaine, 3 gr. to the ounce, deadens the pain. This treatment is especially suitable for children, but should be given to them in $\frac{1}{2}$ -per-cent. solution.

Tartar-emetiic ointment should be dispensed as follows: sterilize white vaselin in a china pot by placing in a saucepan and boiling for ten minutes. Allow to cool. Weigh out the required amount of tartar emetic (1 grm. to every 100 grm. of vaselin for a 1-per-cent. solution), and mix with one or two drops of liquid paraffin on a stone slab. To this mixture add the specified amount of white vaselin, transfer to the china pot and boil up again in a saucepan for fifteen minutes. Allow to cool.

Treatment by X-rays.—When available, this line of treatment appears to be at once rapid and efficacious. In Mesopotamia it is stated that a single full pastille dose of X-rays produces a cure within ten days in the majority of cases. The rays act directly upon the Leishman-Donovan body, penetrating the unbroken skin, and thus being efficient in non-ulcerated as well as in ulcerated sores. This treatment is not followed by any constitutional disturbance, and the scars which are left are hardly noticeable. The apparatus necessary is a coil giving a 16-in. spark with a mercury jet interrupter. Macalaster-Wiggin tubes with 7-in. bulbs were found to be most satisfactory. The rays are directed on to the affected area through a lead glass cylinder; an aluminium filter 3 mm. in thickness being interposed, and the surrounding healthy skin protected by properly shaped pieces of leaded rubber; the Sabouraud unit is used and is estimated by exposing barium platino-cyanide pastilles. The current of the secondary circuit should be 1.25 ma., with a vacuum corresponding to a hardness of 8.9 on the Wehnelt scale. With the

apparatus described, a Sabouraud unit requires an exposure of twelve minutes, which is found in most cases to effect a cure.

Treatment by ionization.—This has been found to give satisfactory results. The ulcer is cleaned and covered with a pad consisting of sixteen layers of lint soaked in 2-per-cent. zinc-sulphate solution; this is firmly applied under a zinc electrode by means of a bandage, and then connected with the positive pole of an electric current which is supplied by eighteen accumulators giving an average of 36–38 volts. A patient with a sore of an area 1 in. in diameter can easily stand 10 ma. as gauged by a resistance coil. The application is continued for twenty minutes, the pad being constantly moistened with zinc-sulphate solution.

Treatment with carbon-dioxide snow.—In Lahore, Central India, the application of carbon-dioxide snow constitutes the sole form of treatment. This should be applied for 5–30 secs., depending upon the size of the lesions; the application is repeated every ten days.

Treatment by injection of emetine.—Photinos reported good results from local injections of emetine hydrochloride, commencing with 0.15 grm., and increasing gradually up to 1.5 grm., into the base of the sore. Sinderson in Mesopotamia uses a 2-per-cent. solution which should be injected so as to reach every part of the sore, so that in large ulcerations it may be necessary to puncture in three or four places. Following the injection the puncture site is sealed with cotton-wool and collodion flexile. When ulceration is deep, healing may not be complete for a month. A local inflammation is thereby set up, with the disappearance of the parasites from the lesion. The lesions usually clear up in fifteen to thirty days.

Other drugs.—Good results have been obtained by the local application of phosphorated oil, by intravenous injections of stovarsol, and in large callous sores, by local application of finely-powdered permanganate of potash. Karamchandani uses subcutaneous injections of berberine sulphate, $\frac{1}{4}$ gr. dissolved in $1\frac{1}{2}$ c.c. of distilled water, in the immediate vicinity of the sore. Two injections, especially when combined with dressings of hypertonic saline, are sufficient.

In specially resistant cases one or more of these methods may be combined.

Prophylaxis.—In the endemic areas of the disease, measures should be taken in the form of insect repellents (*see* p. 97) to protect the exposed parts against bites of phlebotomus. At night-time a fine-mesh netting, forty-five holes to the square inch, is

necessary to exclude these insects. (Fig. 22.) Dogs with suspicious-looking sores should not be permitted in the vicinity of human dwellings. In the East it is still generally believed that infection may be conveyed by laundry which has been washed by natives who are infected with these sores.

III. LEISHMANIASIS AMERICANA

Synonyms.—Espundia; Bubas Braziliana; Uta; Pian Bois; Forest Yaws (British Guiana); Bosch Yaws; Naso-pharyngeal Leishmaniasis.

History and geographical distribution.—Under the names specified, several writers describe a very grave form of leishmaniasis occurring in certain South American countries—Brazil, Bolivia, Peru, Guiana, Martinique, Uruguay and Paraguay, less frequently in Colombia, Venezuela, Ecuador, the Argentine, Yucatan (Mexico), and Panama (Map III); while isolated cases of leishmaniasis resembling the American disease have been reported from the Sudan, Somaliland and Italy. Mutilations of the face reminiscent of this disease have been found in figures engraved on old Inca pottery. In Paraguay the disease has assumed epidemic characters, and a large proportion of the population in certain districts, and 70–80 per cent. of prospecting parties, have become affected, so that most drastic public measures have had to be taken to prevent its spread. It is usually seen in men working in the forests, especially gum-pickers. A similar disease has been observed in the dog in the endemic centres, and it is possible that it occurs in the agouti (*Dasyprocta*).

Symptoms and etiology.—The disease occurs at any age in either sex, in strangers as well as in the indigenous population; it begins as a sore on some mucous surface (Fig. 43). The sore is of the chancreous form of the ordinary oriental-sore type. It heals in time, leaving a characteristic scar. After an interval of months or years, fungating and eroding ulcers (Fig. 44) of a most intractable character break out on the tongue, and in the buccal and nasal cavities, destroying and obstructing them, and ultimately, if untreated by antimony, leading to the death of the patient by exhaustion after years of suffering. The lymphatic glands are often involved, but the abdominal and thoracic organs are spared. Though affecting the mucous membranes in this characteristic manner in the endemic zones, the ulcers, as in oriental sore, occur in other uncovered parts of the body. They have been commonly noted on the pinna of the ear in gum-pickers (*oreja de chichleros*). For the state of São Paulo, Brumpt and Pedroso record localization

of sores as follows (in percentages): Leg 30, foot 12, forearm 12, head 11, hand 10, hip 4, elbow 4, trunk 3, nasal mucosa 3, knee 2, buccal mucosa 2, neck 2, arm 1, pubis 1.

Leishman bodies are to be found, though not in great profusion, in scrapings and sections of the fungating ulcers, and present no morphological differences from *L. tropica* or *L. donovani*, but have been called by Vianna *Leishmania braziliensis*. Giant cells and

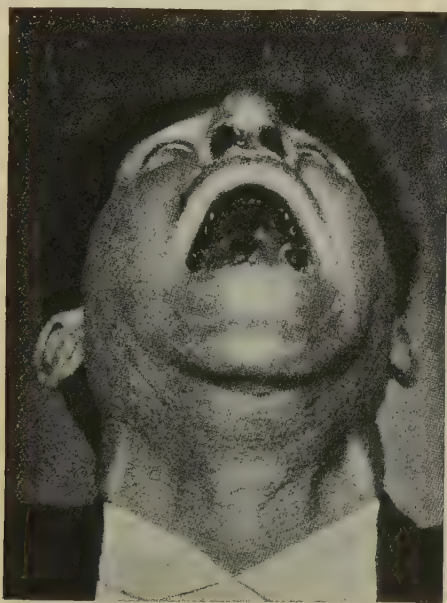


Fig. 43.—Ulceration of hard palate and nares in leishmaniasis Americana. (After Splendore.)

flagellated forms of the parasite have been found in sections. It is believed that the original sore in this grave form of leishmaniasis develops at the site of the bite of a jungle insect of unknown species, possibly a tabanid fly; but since the recent work of the Sergeants on the transmission of oriental sore, a phlebotomus, *P. lutzi*, is suspected of playing a rôle in the spread of the American disease.

Diagnosis is made upon the typical clinical appearances and the discovery of the parasite. Espundia has to be distinguished from the ulceration of yaws (gangosa) and syphilis. In ulcerated

lesions the crust should be removed and smears made from the underlying sero-purulent discharge.

The excision of a piece of granulation tissue and the expression of the contained serum on a slide often afford a more ready method of diagnosis.

Treatment.—The general treatment is the same as for oriental sore, and was first introduced by Vianna in 1913; ten to twenty



Fig. 44.—Ulceration of nares and lips in leishmaniasis Americana. (After Splendore.)

injections of antimony tartrate (20–30 gr.) generally suffice for a cure. The local ulcers on the lips and nose are cleaned up with fomentations, the cleansed surfaces anæsthetized with a mixture of cocaine, menthol, and carbolic acid, then sprinkled with finely powdered antimony tartrate and bound up with a bandage. Subsequently the wounds are dressed with an ointment composed of zinc oxide, bismuth, and lanolin. In the case of the buccal mucosa, scabs must be removed with a solution of bicarbonate of soda, the surface anæsthetized with cocaine (1-per-cent.) and sprayed with 1–2-per-cent. antimony-tartrate solution. Every four to eight

days the tartrate is used in a saturated solution, the application being made by means of a pledget of cotton-wool.

Good results have recently been obtained by intramuscular injections of Eparseno (dioxy-diamido-arsenobenzol), prepared by Poulenc Frères, Paris. Injections of 0.12 to 0.25 gm. (1-2 c.c.) are given and as many as 10-20 injections at intervals of two to three days are necessary to effect a cure. Others have obtained success with similar injections of the double iodide of quinine and bismuth (0.15 gm. daily for one month).

CHAPTER V

DISEASES DUE TO BLOOD SPIROCHÆTES (*TREPONEMA*)

RELAPSING FEVER

Synonyms.—Febris Recurrens ; Spirillum Fever ; Famine Fever ; Tick Fever ; Bilious Typhoid of Griesinger.

Definition.—An acute infectious disease, or, possibly, a group of infectious diseases, characterized by fever of sudden onset and, after several days (one to seven), rapid subsidence, and which may relapse at intervals of from one to seven or more days for an indefinite number of times. It is caused by spirochætes which are present in the blood during the fever and are transmitted by certain insects (body-louse) or by certain ticks (*Ornithodoros*).

History.—Relapsing fever was known to Hippocrates. He mentions the splenic enlargement, the jaundice, the liability to abortion in pregnant women, and the tendency to menorrhagia. In 1873 Obermeier discovered the spirochæte *Treponema* now known as *recurrentis* vel *obermeieri*. In 1904 Philip Ross and Milne in Uganda, and rather later, but independently, Dutton and Todd on the Congo, discovered that in Africa the spirochæte was communicated by the bite of a tick, *Ornithodoros moubata*. The last two observers found that the parasite could pass into the egg and larva, and so confer infective powers on the mature tick of the succeeding generation. In 1907 Mackie recorded an outbreak of relapsing fever in which lice, *Pediculus humanus* var. *corporis* and *capitis*, apparently served as the transmitting agents—a view favoured by the experiments of Nicolle and others. In 1921 Bates, Dunn, and St. John proved that under experimental conditions the ticks *Ornithodoros talajé* and *O. venezuelensis* convey the disease in Panama and in Venezuela.

NOTE ON NOMENCLATURE.—The name *Spironema*, used in former editions of this book for this genus of spirochætes is untenable. It has been pointed out by Stiles that “spironema” is a still-born homonym having been pre-occupied both in zoology and botany.

Geographical distribution.—In Europe relapsing fever occurs from time to time in the British Isles, but especially in Ireland, and in Norway, Denmark, Germany, Russia, and Turkey. In Africa the disease has long been known in Egypt, while Dutton and others found a specially virulent form widely spread in Central Africa (tick fever) in the Congo, East Africa, Uganda, Abyssinia, and Madagascar. In Asia it is met with in Persia, and in India, where in 1922 large epidemics occurred in the Central Provinces

and North-western Frontier. It is of frequent occurrence in China. Epidemics have been recorded in the United States, and recently in Senegal and French Equatorial Africa, while a special tick-borne form of the disease has been known since 1909 in the northern states of Central and South America.

Etiology.—It has been definitely proved that the various forms of relapsing fever are caused by *Treponema recurrentis*, and organisms which are morphologically indistinguishable from it, but which may be biologically distinguishable, such as *T. duttoni* and *T. venezuelense*.

Typically, the *treponema* is a delicate spiral filament, averaging $17\ \mu$ in length (extremes $5\text{--}36\ \mu$ by $0.25\ \mu$). Formerly, with appropriate staining, a flagellum was described, but this is not now generally accepted as correct (Nuttall). The body of the parasite may have three, four, or six bends or turns; dividing forms appear to have more; in fact, the body of the spirochæte undulates, it does not strictly form a spiral. By the Romanowsky method the body of the parasite usually stains uniformly, with the exception of the extremities, which are pointed and take only a very faint tint. In fresh blood the spirochætes exhibit very active screw-like movement; some are longer than others, the long forms resulting from end-to-end attachment of two or more parasites. That this is the explanation of the long forms, which may measure from 16 to $100\ \mu$, is shown by staining. In those measuring from 16 to $18\ \mu$ we find a pointed extremity at each end of the filament and a pale zone in the middle, the pale zone corresponding to the approximated lightly staining extremities. The still longer forms admit of a similar explanation. Although the normal habitat of the spirochætes is the liquor sanguinis, occasionally in fresh liquid blood preparations they are seen within the red blood-corpuscles, though this probably does not occur within the body.

Great variation is shown in the morphology of the *treponemata*, but there is a consensus of opinion now that no constant morphological distinctions exist between the organisms occurring in the different clinical forms of the disease. For an explanation of the nomenclature the reader is referred to p. 708.

Demonstration of the parasite.—It is necessary to remember that the parasite occurs in the blood during the febrile stage of the disease only, often disappearing forty-eight hours before the crisis and being very scarce or absent entirely during the non-febrile intervals. In some forms and cases of the disease it is present in large numbers in every field of the microscope; in other forms and cases it is so scanty that many fields have to be examined before a single specimen can be discovered. In thin films of fresh blood its presence can usually be recognized from the agitation its movements communicate to the adjacent corpuscles. (Fig. 45.) In dried and fixed films the stains in general use for malaria work suffice.

It has been pointed out that it is especially in children that the spirochætes may be found, in the blood-stream during the apyretic periods.

The dark-ground method of illumination is admirably adapted for demonstrating these parasites in a living state; a very strong illuminant, preferably a high-power electric light—not always procurable in the tropics—is required. Occasionally, when very scarce in the blood-stream, as during a relapse, or in the clinical form of the disease met with in North Africa, the organism may best be demonstrated by the “thick-film” method.

Systematic position of the treponema (see p. 708).—Until recently, biological opinion was unsettled as to the exact status of the treponema—whether it belongs to the bacteria or to the protozoa. The argument for its bacterial nature was founded on its mode of division, which is by transverse fission only (Wenyon).

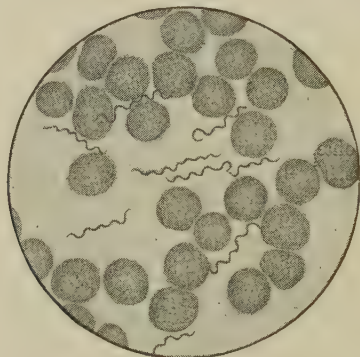


Fig. 45.—*Treponema recurrentis* in blood-film. $\times 500$.
(Microphoto: Dr. John Bell.)

Cultivation.—The successful cultivation of *T. recurrentis* and its subvarieties has been effected by Noguchi and others in sterile ascitic fluid containing citrated blood and a small amount of fresh kidney, incubated at 37° C. The greatest multiplication of the organisms takes place at the junction of the ascitic fluid and of the blood. The treponemata reach their maximum development on the seventh to the ninth day, after which they begin to disintegrate. Subcultures retain their virulence for mice.

Different strains of relapsing-fever parasites.—It is undoubtedly the case that in one part of the world the treponema of man is transmitted by one species of blood-sucking arthropod, and in another part of the world by another; that the serum reactions of these parasites differ; and that the fevers they cause are, in some respects, different clinically. The parasite, as originally described in Europe, is known as *T. recurrentis*. Attempts have been made to separate the North American form under the name of

T. novyi, the Indian form as *T. carteri*, and the North African form as *T. berberum*, though these distinctions do not appear to be valid. The parasite of the Persian form of the disease (mianeh fever), which is thought to be clinically distinct, is known as *T. persicum*, that of the Central African disease, popularly known as tick fever (or carapata disease), as *T. duttoni*. The South American form is known as *T. venezuelense*; that of Panama as *T. neotropicalis*. In 1926 de Buen described in Spain a new variety more resembling the Central African form which is transmitted by a tick (*O. maroccanus*), and the parasite has been called *T. hispanicum*. A synopsis of these varieties and the diseases they produce follows:

SYNOPTICAL TABLE OF VARIOUS STRAINS OF TREPONEMA AND CLINICAL SYMPTOMS OF THE RELAPSING FEVERS THEY EVOKE IN MAN

Habitat and strain.	Cosmopolitan: N. America, N. and W. Africa, Europe, India, Southern States of S. America. <i>Treponema recurrentis</i> (obermeieri).	Persia and N.-West India. <i>Treponema persicum</i> .	Central Africa. <i>Treponema duttoni</i> .	Central and S. America (Colombia and Venezuela). <i>Treponema venezuelense</i> .
Animals susceptible.	Small rodents, only after passage through monkeys.	Gerbilles. Monkey (<i>Cercopithecus</i>).	Small rodents and many animals susceptible.	Rats and monkeys (<i>Macacus</i>).
Course in animals.	Mild.	Very mild.	Very severe.	Severe.
Subinoculations in animals.	Monkey to monkey, mouse to mouse, positive.	Gerbille to gerbille.	Monkey to monkey, positive. Same for most animals.	Rat to rat.
Course in man.	2-5 relapses. Incubation period 2-10 days. Duration of attack 5-6. Apyrexia 7-10.	Fairly severe attack, usually short, average 2-6 days. Relapses 2-3, sometimes 7.	Severe: 2-11 relapses. Incubation period 7-10 days. Duration of 1st attack 3. Apyrexia 1-8. Complications severe.	Apparently resembles the Central African form.
Natural transmitters.	Lice (<i>P. humanus</i>).	Ticks (<i>O. tholozani</i> , <i>O. lahorensis</i>). ¹	Ticks (<i>Ornithodoros moubata</i>).	Ticks (<i>Ornithodoros venezuelensis</i> and <i>O. talajé</i>).
Serum reactions.	Immune serum not agglutinating <i>T. duttoni</i> .	Immune serum not agglutinating <i>T. recurrentis</i> .	Immune serum not agglutinating <i>T. recurrentis</i> .	Immune serum not agglutinating <i>T. duttoni</i> .

¹ De Buen has recently described the parasite of Spanish relapsing fever as *T. hispanicum*, which is transmitted by *Ornithodoros maroccanus*, an inhabitant of pig-sties. In Dakar several wild rodents, especially shrews, rats and mice, have been found naturally infected with an organism indistinguishable from the *T. recurrentis*. These animals, then, may act as natural reservoirs of the infection.

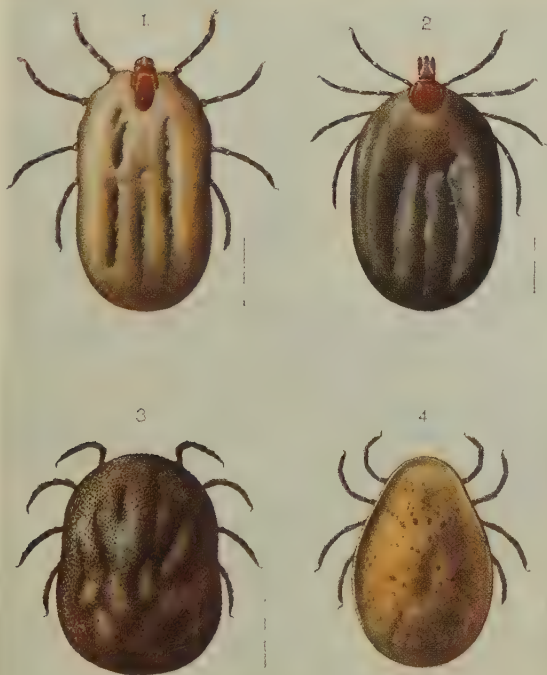
Pathology.—The spleen is usually large and soft, and often shows multiple infarcts and fibrinous exudates; it may rupture spontaneously during life. Liver, kidneys, and heart show cloudy swelling of their cellular elements. The skin in fatal cases is usually jaundiced, and there may be subcutaneous petechiæ. The bone-marrow is hyperæmic, and shows great activity of the leucoblastic elements. There is generally a marked polymorphonuclear leucocytosis, and the spirochætes, very numerous, often phagocytosed, are found in the spleen and bone-marrow. In microscopical sections of the spleen and liver the spirochætes are seen in great numbers within the endothelial cells—an observation which suggests that the parasites retire to these organs during the apyrexial periods. The spirochætes rapidly disappear after the patient's death. During the apyrexial periods an occasional parasite may be found in the peripheral blood by injecting intraperitoneally not less than 25 c.c. into a susceptible animal, which must be examined twice daily for the succeeding ten days before a negative result can be declared.

In Germany and Austria stains of relapsing fever spirochætes have been used for therapeutic inoculation in the same manner as malaria. Some facts of importance have emerged as the result of this study: that the spirochætes may be demonstrated in the liver, brain and cerebro-spinal fluid and that active infection may be produced by inoculation of susceptible animals with material obtained during the quiescent periods and even after apparent recovery from the disease.

Mode of transmission.—There are two main forms of intermediary host which transmit relapsing fever, namely lice and ticks. The form of fever as it occurs in Europe, Asia, and North America is conveyed by lice (*Pediculus humanus*). The Persian form, *T. persicum*, is said to be transmitted by ticks, either *Ornithodoros lahorensis* or *O. tholozani*, though this statement rests solely upon epidemiological evidence.¹ Tick fever, the Central African form, is undoubtedly transmitted by another ornithodoros, *O. moubata*. (Plate XI, Fig. 3.) The analogous disease of Central and South America is conveyed by *O. venezuelensis* and *O. talajé*. According to de Buen, *O. maroccanus* transmits relapsing fever in Spain.

Epidemiology and endemiology.—The fevers caused by *T. recurrentis* occur, as a rule, at definite seasons of the year, depending upon the circumstances which favour the propagation of their intermediary host, the body-louse. In times of peace the poorer and more indigenous class of the community are attacked. In

¹ The statement made in previous editions of this book, that the tick *Argas versicus* may carry the disease, rests on somewhat insecure evidence.



1, *Margaropus (Boophilus) annulatus* (partially distended);
 2, *Ixodes reduvius* (partially distended); 3, *Ornithodoros*
moubata; 4, *Argas persicus*.

FEMALE TICKS.

PLATE XI

Europe, for instance, relapsing fever has been a feature of times of famine. This has long been noted in Ireland, where it is known as "famine fever," and during recent years widespread epidemics have occurred among the famine-stricken population of Central Russia. In war-time it is the scourge of armies in the field, and is commonly associated with epidemics of the dreaded typhus, itself a louse-borne disease. The two infections may coexist, as was noted in the great Serbian epidemic of 1915. In southern Europe and northern Africa relapsing fever is a disease of the winter and spring months, at which time the natives are wont to envelop themselves in thicker clothes than usual and to congregate together for the sake of warmth, thus facilitating transmission. The louse-borne disease is uncommon in Equatorial Africa, where, on account of the scantier clothing worn, this insect is unable to thrive. In India it has been noted that at the advent of the hot weather, in April and May, the lice die off and the epidemics of relapsing fever come abruptly to an end. A particularly virulent epidemic of *louse-borne* relapsing fever commenced in French West Africa in 1921, and raged till 1924. During its course it spread to Senegal and the French Sudan, and extended southwards to the Gold Coast and Nigeria. It is thought by some to have been introduced by repatriated Senegalese troops from Syria. In 1926 this relapsing fever appeared in Darfur, the most westerly province of the Anglo-Egyptian Sudan, and caused the death of 10,000 out of a population of 45,000.

The tick-borne forms of relapsing fever differ considerably from the foregoing, in that the infection is transmitted hereditarily by these arthropods, and the infection is confined to houses and localities which afford a suitable environment for *Ornithodoros*. In Central Africa it has been known for many years that the "rest-houses" on the main routes of travel are endemic centres of tick fever, for the ticks live in the mud walls and roofs of the huts, and emerge at night-time to feed on man. There is therefore no seasonal incidence in this disease, as occurs in the other forms of relapsing fever. The same has been noted in the South American form, except that a greater incidence of the disease is observed in the wet and rainy season, when native labourers and oil prospectors are necessarily more confined to their quarters than during the finer months of the year.

Evolution of the parasite in the intermediary host.—Philip Ross, Milne, Dutton and Todd have definitely shown that *T. duttoni* is normally conveyed by the tick *O. moubata*, and that it can be transmitted not only by the insect which has bitten the infected individual but also by its progeny, even to the third

generation (Koch); thus, as noted above, the spirochæte has actually been demonstrated within the eggs laid by infected ticks. From these eggs nymphs are produced in which the spirochæte multiplies in large numbers. Once fed on spirochæte-containing blood, ticks remain infective for one-and-a-half years, and can convey by successive bites relapsing fever infection to at least ten monkeys.

Development in the tick.—According to Leishman, the spirochætes remain motile for several days after ingestion by the tick (*O. moubata*), the duration depending upon the atmospheric temperature; they then lose their motility and break up into chromatic granules which clump together in the Malpighian tubules of the tick. Should the temperature be raised, a crop of young spirochætes develop from the granules and then disappear suddenly. It would appear that recurring multiplication of the spirochætes takes place in the tissues of the tick in much the same way as in man. The Malpighian tubes act in this case as culture-tubes, the organisms being subsequently passed out in the fæces of the insect. The entrance of the spirochæte into the human skin is aided by the irritation caused by the bite, which provokes scratching and consequent inoculation of the deposited spirochætes; this is facilitated by the fluid exuded from the tick's coxal glands which dilutes the fæces. According to Nicolle and his co-workers, *T. duttoni* cannot be transmitted by lice. Other observers do not agree that the development proceeds in the exact manner described above, but regard it as identical with the developmental stages seen in the louse.

There has been a great controversy as to the meaning of the chromatic granules seen within the body of the tick, but it is probable that these are the two kinds, some representing a degeneration of the defunct spirochætes, while others are to be regarded as active stages in the developmental cycle of the organism. The fact remains that for a considerable time after ingestion, fully-formed spirochætes cannot be demonstrated within the body-cavity of the infected tick. Wenyon states that the granule stage of the parasite in the tick has not been definitely proved.

Development of the parasite in the louse.—The spirochætes in the stomach of the louse alter very rapidly, and disappear within twenty-four hours at a temperature of 78° F. The so-called "metacyclic" organisms appear in great numbers on the sixteenth day in the body-cavity; at the end of this time the organisms are more slender and, as a rule, shorter than those found in the blood, but they develop to their full size in a few days' time. (Fig. 46.) Thus it has been proved that the lice become infective on the sixteenth day, and the infection is probably conveyed by the fæces of

the louse, or by the actual crushing of the insect on the excoriated skin. The infection may also be conveyed on the fingers and gain entrance through the conjunctiva. Under optimum conditions, 43 per cent. of lice become infective and remain so for twenty-eight days. There is no conclusive evidence of hereditary transmission in the louse.

Other methods of transmission.—The spirochætes have been proved to be capable of penetrating the mucous membrane and, if well rubbed in, the unbroken skin. Nurses and doctors engaged in treating relapsing-fever patients have been inoculated with the

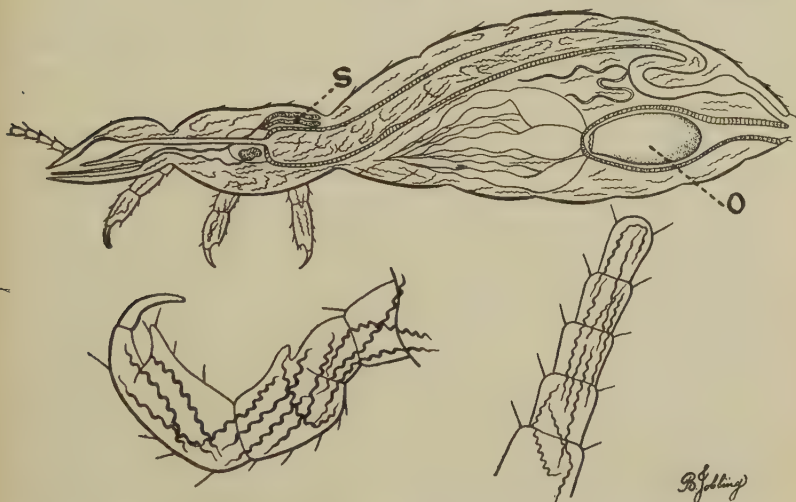


Fig. 46 —*Treponema recurrentis* of relapsing fever, and its development in louse (*Pediculus humanus*). (C. M. Wenyon, "Trans. Roy. Inst. of Gt. Brit.")

Diagram shows whole body invaded by spirochætes. S, salivary glands; O, egg. Below, spirochætes in leg and antenna, which are easily broken off, so that fluid exuding from body infects skin of host.

disease through the entry of infected blood into the conjunctival sac, and in the case of pregnant women and experimental animals it has been proved that the organism can pass through the placenta to the foetus.

White mice and white rats are especially susceptible. The former are particularly so, the organisms appearing in the blood within twenty-four hours of inoculation and persisting to the third day. About this time they disappear for several days from the blood until the commencement of the first relapse, which may be followed by a second, third, or even a fourth, the number varying

in individual mice; with each relapse the parasites reappear in the blood. The interval between the relapses is generally about seven days; occasionally it is only two, though it may be as many as ten. The actual number of organisms in the blood in the first is greater than in subsequent relapses, indicating the development of a partial immunity. Recovery in mice is the rule.

As a result of the consecutive passage of the spirochæte through a long series of rats, its virulence is augmented, so that the incubation period becomes reduced to 15-18 hours, and the persistence of the parasite in the blood is prolonged to 60 hours instead of, as originally, 48 hours; at the same time the spirochætes become far more abundant.

In rats an acquired immunity may be produced which lasts for many months. As a rule, *T. duttoni* produces a far more severe disease in these animals than does *T. recurrentis*.

Rabbits and guinea-pigs are relatively refractory.

As regards *T. venezuelense*, South American monkeys, dogs, rats and guinea-pigs are refractory. Man appears to be the chief reservoir of the virus. Mice which have been rendered immune to *T. duttoni* are subsequently capable of being infected by this spirochæte.

Immunity.—Sabritschewsky, in 1896, showed that when equal parts of spirochæte-infected blood or serum, and normal serum are mixed, the spirochætes survive longer than when the infected blood is mixed with that of a patient who has recovered from relapsing fever. He accordingly concluded that the cause of the crisis in relapsing fever and of subsequent immunity was the development of a germicidal substance in the blood. He was the first to apply serum-therapy in the treatment of relapsing fever. He obtained an anti-spirochæte serum by repeated inoculation of the horse with human spirochæte-containing blood. The value of this serum was successfully established by Löwenthal; of 87 patients treated, 43 (49 per cent.) recovered without a relapse.

Treated *in vitro* with hyperimmune serum, the spirochætes rapidly become unrecognizable aggregations of granules, and this phenomenon may be manifest in a dilution of 1:2,000.

Cunningham in 1925 showed that spirochætes which cause the first attack differ serologically from those which appear in the first relapse, but agree with those of the second relapse. There is thus an alternation of serological stains. It is probable that the antibodies produced in the blood-stream by one particular stain do not persist long enough to prevent relapse from taking place.

GENERAL SYMPTOMS COMMON TO ALL FORMS

COSMOPOLITAN TYPE—The course and character of the disease vary greatly in a single epidemic, and, further, the virulence of the more severe forms is much greater in some outbreaks than in others. The *incubation period* usually lasts from two to ten

days. In some instances the attack develops promptly on exposure; it is never delayed beyond the fourteenth day. In the artificially inoculated, symptoms show themselves in from two to six days.

The *onset* is generally abrupt, being characterized by chilliness or rigor, giddiness, epistaxis, vomiting, photophobia, and intense headache. In the young there may be convulsions. Temperature rises rapidly to 104° or 105° F., sometimes to 108°. (Chart 7.) The pulse is rapid, 110 to 130. Should fever run high, there may be delirium. The skin is dry, although, especially during the first day, occasional sweats may break out. A slight icteric tinting of the conjunctiva is usual; not infrequently jaundice is marked at the crisis. The spleen is invariably enlarged and tender. The tongue is coated and moist, except in bad cases, in which it may become dry and brown. The bowels, as a rule, are confined; abdominal pain may be considerable. Occasionally herpes labialis is noted, and in certain epidemics a rash of rose-coloured spots on the trunk and limbs has been observed; some authors describe petechiæ. The rash has a peculiar distribution, being generally most marked in the region round the neck, spreading in a semicircular fashion from the tips of the mastoid processes; thence it ranges in a symmetrical manner round the shoulders, down the sides of the chest and abdomen to the inner aspect of the thighs, and to the extensor and flexor aspects of the forearms. The individual petechiæ may be as large as a threepenny bit, and need to be carefully differentiated from the exanthems of typhus and hæmorrhagic smallpox.

This, the primary remittent fever, may last from five to seven days. At first the morning is usually lower than the evening temperature, but on or about the third day the evening temperature rarely rises above that of the morning. On the fourth, fifth, or sixth day there is again a rise of temperature, sometimes with delirium, ending in a crisis of profuse sweating and diarrhœa. The temperature now falls rapidly to normal or subnormal, sometimes dropping in the course of a few hours as much as 12° F.; in the latter event, especially in elderly or delicate patients, there may be dangerous collapse.

The initial pyrexia, called *first paroxysm*, is followed by a *first period of apyrexia* during which the patient recovers so rapidly that after four or five days it may be difficult to keep him in hospital. But from seven to nine days after the crisis, that is about the fourteenth from the commencement of the attack, rigor again occurs, followed by a second attack of fever—*first*

relapse. This may be more severe than the initial paroxysm; usually it is milder, and seldom lasts so long. During its continuance the secretion of urine is considerably increased; sweating also is profuse, and prostration marked. An absolute polymorphonuclear leucocytosis of 15,000 and over is found during the pyrexial periods.

With the defervescence of the first relapse the patient enters on the *second period of apyrexia*, which is usually coincident with convalescence. (Chart 7.) But in some patients a *second relapse* may occur, usually about the twenty-first day, counting from the commencement of symptoms. This second relapse rarely lasts

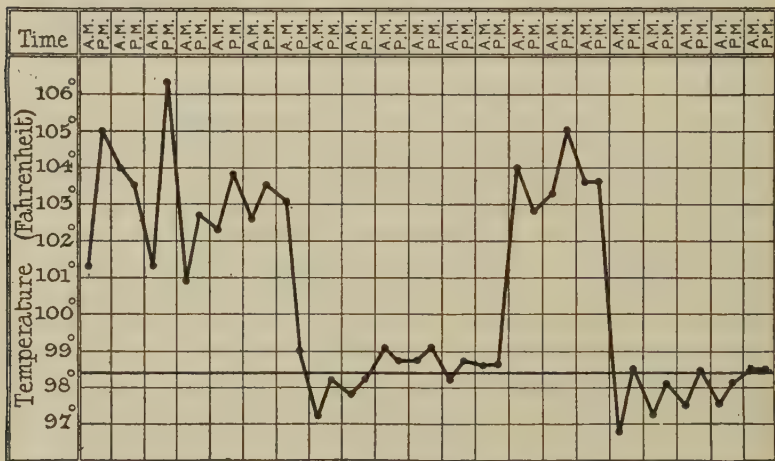


Chart 7.—Relapsing fever, European type. (Orig.),

longer than three days, and is generally milder than the previous paroxysms. In rare instances three, four, five or even more relapses have been observed. Anomalous types of fever are common. Some temperature charts show an intermittent fever throughout, more resembling that of phthisis than anything else. Cases with four relapses in a period of twenty-six days are met with. Occasionally the apyrexial period may be of considerable length—seventeen days; in one case observed, forty-two days,

Convalescence may be protracted, and complicated with such sequelæ as nephritis, ophthalmia, otorrhœa, polyarthritis, pneumonia, neuritis, parotitis, adenitis. In pregnant women abortion is the rule.

BILIOUS TYPHOID TYPE.—This type is thought by some to be a distinct disease and, on account of the severity of its symptoms and

African campaign by J. K. Manson and Thornton. In these the spirochætes occur in enormous numbers ; coma and death may ensue within twenty-four hours. Sometimes there is most intense icterus. These observers consider that death is brought about by the impaction of masses of spirochætes in the cerebral capillaries.

In natives of the endemic districts the disease, as generally observed, is not nearly so severe as in Europeans and strangers, being usually limited to a paroxysm or two of one or two days' duration. The mildness of these attacks is probably explained by a partial immunity conferred by previous attacks.

Implication of the central nervous system is a not uncommon complication. Some observers have described aphasia, facial paralysis, hemiplegia, and implication of the cranial nerves—such as the third, fourth, and sixth (resulting in ptosis and strabismus), the fifth (trigeminal neuralgia), the seventh (facial paralysis), and the eighth (deafness)—as coming on suddenly during the course of the disease. In these nervous complications the spirochætes may sometimes be demonstrated in the cerebro-spinal fluid ; as a rule it contains an excess of lymphocytes and is under considerable pressure, necessitating lumbar puncture in order to relieve symptoms. In patients infected with subtertian malaria a superimposed attack of relapsing fever may determine the onset of blackwater fever.

CENTRAL AND SOUTH AMERICAN TYPE.—As far as is known, this fever resembles in almost every particular the Central African form described above.

Mortality of relapsing fever.—The death-rate is usually below 6 per cent. In a serious form with jaundice, which has been noticed on the West Coast of Africa, the death-rate may exceed 50 per cent. In the feeble and old, death may ensue at the height of the first paroxysm, or from exhaustion as the result of relapses.

Diagnosis.—This fever is most usually confounded with subtertian malaria, from which it may be indistinguishable on clinical grounds ; it may also resemble infectious jaundice, enteric, typhus, influenza, dengue, pneumonia, malignant smallpox, and even plague. In South America and West Africa it may be confused with yellow fever. The detection of the spirochætes with the microscope, or by animal inoculation, is the most reliable method of diagnosis. They are readily demonstrated with the dark-ground illumination ; for methods of staining, see p. 885. At an early stage the relapsing character of the fever is not available as an aid to diagnosis, but at a later period the history of a fever

which had relapsed about fourteen days from the onset of the disease should be regarded as highly suggestive.

Wassermann reaction. — A strong positive complement-deviation is obtainable, both during the pyrexial stage and in the apyretic periods between the early relapses, in about 20 per cent. of cases (Fairley). This apparently applies to all clinical types of the disease.

Treatment.—Careful nursing and dieting are necessary, especially in the African type, and must be maintained after the crisis, when the patient is ravenously hungry. In *salvarsan and its allied preparations* we have a specific. The one selected should be given by the intravenous route in doses of 0·3 grm. to 0·9 grm., according to the age of the patient and the severity of the case, the dosage being reckoned as 0·01 grm. for each kilogram of body-weight. After a short aggravation of the symptoms a crisis takes place with the disappearance of the spirochaetes from the blood, and, in the vast majority of cases, recovery. Should relapse occur—a rare event—a second injection may be given. Of the salvarsan compounds, undoubtedly novarsenobillon is the best; neosalvarsan, luargol, arsaly, kharsivan, galy (0·35 grm.), and salvarsan are useful in a descending order of merit, and recently sulphoxyl-salvarsan (Höchst), has given good results. The latter preparation, as also sulphostab (Boots), in doses ranging from 0·3 to 0·6 grm. has the additional advantage that it may be given by the intramuscular or deep subcutaneous routes. Evidence shows that the drug is most efficacious when given in the pre-critical days—that is, when the temperature is on the rise, directly the diagnosis has been made. Relapses are apt to occur if it is given while the temperature is *on the fall*, or during the apyretic period; this is especially true of the Central African type, some cases of which appear to be specially resistant to salvarsan treatment. If it is not given in the first attack, one should wait till the first relapse, and then give it on the rise of temperature. Salvarsan ought not to be given when the crisis is imminent: a very grave reaction, due to the great destruction of the spirochaetes and the liberation of their toxins, with corresponding aggravation of the symptoms and, it may be, fatal collapse, is apt to ensue. On the other hand, the great majority of otherwise healthy patients recover from most forms of relapsing fever without specific treatment at all, although, on account of relapses, convalescence may be prolonged. Albuminuria should not constitute a contraindication to salvarsan treatment. *Stovarsol* tablets (4 gr.) in doses of six daily are said to be singularly efficacious in relapsing fever,

when, for some reason or other, intravenous injections cannot be undertaken.

The collapse and fall of blood-pressure with subnormal temperature which follow the crisis have to be counteracted by strychnine, brandy and intrarectal douches of hot salines.

From Tanganyika Territory it is reported that sometimes intravenous injection of mercurochrome (20 c.c. of a 1-per-cent. solution) is more beneficial than that of salvarsan.

Prophylaxis.—In the louse-conveyed forms of relapsing fever, prophylactic measures are necessarily aimed at the destruction of lice and their eggs by all the measures known to sanitary science—often a matter of very considerable difficulty when dealing with large groups of native porters or labourers, especially during the rainy season. This disinfection is best performed by means of superheated steam in a portable Thresh's disinfector, or in specially constructed cars in a disinfecting train, the superheated steam being supplied by the locomotive (Stammers). As head lice can convey relapsing fever in the same manner as the body pediculus, local measures, such as application of *oil of sassafras* to the head, must be undertaken.

In the African form, prophylactic measures are much more difficult, and necessitate an intimate knowledge of the habits of *Ornithodoros*, which does not live on the body of its victim, but emerges at night-time from the native houses to feed on blood. It is also found on the veld living in the burrows of the wart-hog, but as a rule it is only met with in numbers in the vicinity of old camping sites (*see* p. 797). The *ornithodoros* itself is very difficult to destroy, and may remain uninjured after prolonged soaking in cresol.

The following rules are necessary :—

1. Avoidance of native houses, most of all at night-time—especially those situated on much-frequented routes of travel. Bedsteads of native manufacture should also be avoided. Camps should be placed as far distant as possible from native villages.
2. Avoidance of much-frequented ground for camping sites; it must be remembered that *Ornithodoros* can exist without food for years. Sleeping on the ground should not be practised unless absolutely necessary, and only when well protected by a mosquito-net. The use of a nightlight is recommended to scare away the ticks. Blankets should be carefully inspected before retiring to rest.

Native huts should be so constructed that a space of 8-10 in. intervenes between the walls and the ground. Mud and rubble buildings are inadvisable; floors should be raised, and made of cement. A deep trench dug round a building and filled with wood-ash has been found effective in excluding ticks.

Children especially act as a reservoir of the virus, and the ticks feed upon them.

For a description of the ticks (Plate XI) and their habits, *see* p. 795.

CHAPTER VI

DISEASES DUE TO BLOOD SPIROCHÆTES (*LEPTOSPIRA*)

DURING recent years it has become possible to group certain fevers together which have certain clinical features in common through the discovery that certain delicate spirochætes (*leptospiræ*) are present in the blood-stream and in various viscera. Under the heading of *Leptospirosis* are included infectious jaundice and seven-day fever.

INFECTIOUS JAUNDICE

Synonyms.—*Icterus Gravis*; Weil's Disease; *Spirochætosis Icterohæmorrhagica*; Mediterranean Yellow Fever; Griesinger's Disease; *Odan-eki* (Japanese).

Definition.—A severe form of fever caused by *Leptospira icterohæmorrhagiæ*, associated, though not invariably, with jaundice, enlargement of the liver and sometimes of the spleen. The natural reservoir of infection would appear to be the rat (*Rattus rattus* and *R. norvegicus*).

History.—An acute febrile illness associated with jaundice and a high mortality was first described by Weil in 1886, and has since been known as Weil's disease. In 1915 Inada, Ido, and other Japanese investigators described the spirochæte *L. icterohæmorrhagiæ* as the cause of the disease, and this was confirmed in Germany by Huebener and Reiter in the same year. In the early summer of 1916 this disease occurred sporadically among the allied and enemy troops in France, and the Japanese discovery was soon confirmed by Stokes, Ryle, and Tytler among British troops, and by Uhlenhuth and Fromme on the German side, while Bonini recognized it on the Italian front. In 1917 the same Japanese investigators, by means of guinea-pig inoculations, proved the presence of the *leptospira* in otherwise healthy rats (*R. norvegicus* and *R. alexandrinus*) and in the field-vole (*Microtus montebelloi*).

Geographical distribution.—The disease appears to be especially prevalent in Japan; during the Great War, outbreaks occurred among the troops in Gallipoli and Salonika, and also in Egypt, where the disease had long been known to exist. It is found along the North African coast and the shores of the Mediterranean. It

is known to occur in France, Italy, Germany, Holland, the United States, Peru, and Brazil, and is endemic in West Africa, the Congo, and the Sudan. Epidemics have been recently described in the Andaman Islands and in the Malay States (Fletcher). The form of the disease as it occurs in the tropics is said to be more virulent, though further researches on this point, as well as on its distribution in hot countries, are necessary. In Europe it is said to be more common in summer-time. The Editor, in 1922, recorded a case in London, and others have been observed in coal-mines in Scotland.

Epidemiology and endemiology.—In Japan the disease has a definite seasonal incidence, occurring, as a rule, most frequently in the months of September to November. In Europe it occurs most often in the hot summer months. The organism is found as a harmless parasite in the kidneys of wild rats and mice, and is excreted in their urine; and the disease is usually endemic among farmers and miners who are exposed to wet soil and water conditions, such as prevailed in the trench warfare and caused the epidemics of 1916 and 1917 in France.

In some cases the water itself appears to constitute the source of infection, and epidemics have been recorded as occurring among soldiers in Italy and in Germany after bathing in certain river pools. It is now known that spirochætes of the leptospira type are widely distributed in water, and some of them have been proved to be pathogenic on inoculation into guinea-pigs (Zuelzer). Accidental inoculation through the conjunctival sac has been observed.

The disease occurs in dogs, especially fox-hounds, in which it is known as "the yellows," and it has been recognized in the fox and in leopards.

Etiology.—*L. icterohæmorrhagiæ* is found in the blood, urine, cerebro-spinal fluid, and sputum. It is a spiral filament with wide flexures, the individual spirals being in close apposition (Fig. 47). The largest forms attain a length of $20\ \mu$ by $0.25\ \mu$, the average length being $6-12\ \mu$.

It is doubtful whether there are any morphological features by which the organism may be distinguished from *L. icteroides*, originally described by Noguchi in yellow fever. The majority of workers now regard the organisms as identical. The organism may be demonstrated by the dark-ground illumination, but is so extremely active that its movements can only be detected with difficulty. According to Fletcher, they are most easily demonstrated in blood-films by Fontana's method. Although easily found in the blood of guinea-pigs, they can be found in man only

with great difficulty. In microscopic sections of infected organs the leptospiræ show up well with Levaditi's method of silver-nitrate impregnation.

The organisms exhibit rapid movements: when free, one end is extended and straight, the other semicircularly hooked, so that they progress in the direction of the straight portion and appear to be propelled from the rear by the rotating hook.

This parasite has been cultivated by Noguchi on solid media such as blood-agar or gelatin (see p. 861). According to Fletcher, the organism grows readily on agar impregnated with immune serum, but is agglutinated thereby in a peculiar manner.

According to Fletcher and Brown, there are distinct serological races of *L. icterohæmorrhagiæ*, the Andaman and Sumatran strains being distinguishable from those found in Europe and elsewhere.

The natural reservoir of the leptospira appears to be the rat, in which it occurs in the fæces, urine, and kidneys, though it has not yet been demonstrated in the blood. It is believed that the

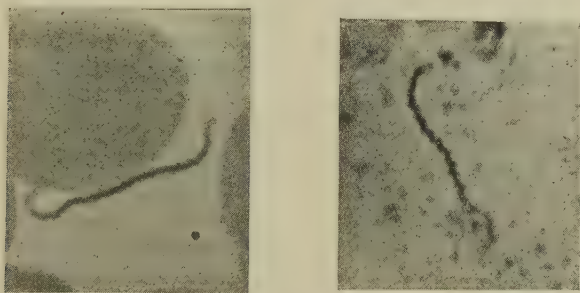


Fig. 47.—Microphoto of *Leptospira icterohæmorrhagiæ* from kidney of rat.
× 3,000. (Dr. A. C. Coles.)

disease was originally epizootic in rats, but that these animals have now become tolerant. In Japan the leptospira has been demonstrated in 32.4 per cent. of wild rats; to a less degree in France, Tunis, and Algiers; and in 4 per cent. of sewer-rats in London (Foulerton). *L. icterohæmorrhagiæ* has been demonstrated by Buchanan in the zoogloea-like "roof-slime," which thus constitutes the source of infection in certain coal-mines in Scotland. Probably the portal of entry is through skin abrasions; guinea-pigs have been infected by rubbing in cultures through the depilated skin. Water is probably the main source of infection.

Guinea-pigs are very susceptible to infection, and so, also, but to a less degree, are dogs and puppies, rabbits and monkeys. In order to reproduce the disease in these animals, 3-5 c.c. of

the patient's blood are required, and should be injected intraperitoneally, when the animal dies of intense jaundice about the tenth day.

Pathology.—The liver is invariably increased in size, and may weigh 100–150 oz. The gall-bladder is generally half-filled with brown or greenish-brown bile; no blockage of the biliary ducts has been ascertained. The various microscopic lesions are reducible to three main types. In the first there is little destruction of the parenchyma or intercellular tissue; the second is characterized by extreme cellular degeneration; in the third there is a localized destruction of glandular tissue. The fatty degeneration of the liver in Weil's disease is moderate in degree, but cannot compare with that seen in acute yellow atrophy. The leptospiræ can be demonstrated in large numbers by Levaditi's method among the secretory cells of this organ. The spleen may be enlarged and the glandular substance soft and diffuent. A generalized enlargement of the lymphatic glands, especially at the hilum of the liver, with hyperplasia and multiplication of the mononuclear cells, has been noted. Hæmorrhages occur in the kidneys, mostly in the intertubular tissues; later in the disease the microscopic picture may resemble that of early interstitial nephritis, and the leptospiræ may be demonstrated in great profusion. The bone-marrow exhibits considerable changes, proliferation of the myelocytes, deposition of pigment in the macrophage cells, and diminished activity of the hæmatopoietic system being the chief features. There are submucous petechiæ in stomach and duodenum, and hæmorrhagic patches in the lungs. The number of the red blood-corpuscles diminished is about two million per c.mm., with a corresponding reduction in the hæmoglobin. There is said to be an enormous reduction in the number of blood-platelets, to 10,000 per c.mm. (normally 200,000); the coagulation-time of the blood is increased to twenty minutes.

Inoculated guinea-pigs and puppies show in a marked degree this tendency to hæmorrhage. The interstitial hæmorrhages into the lung impart a characteristic appearance to that organ, the so-called "butterfly lung."

Symptoms.—The *incubation period* in experimental animals is from five to six days. In man the *onset* is acute, with rigors, vomiting, headache, diarrhœa, and abdominal pains. A few hours later, fever ensues, with thirst and a general aching of the limbs. There is intense injection of the eyes which may constitute the earliest and most striking feature. The intense prostration, the almost agonizing muscular pains and aching of the bones constitute the most distressing features of the illness. The pyrexia is of an

irregular type, between 103° and 105° F., falling by lysis in severe cases about the tenth or eleventh day. There is usually a secondary and terminal rise of temperature lasting three to nine days, which is associated with the excretion of the leptospiræ from the urinary tubules. Convalescence is established in the third week. Jaundice, which occurs in 50 per cent. of cases, when present, is noted in from forty-eight to seventy-two hours from the onset, and may be ushered in by hæmorrhages into the conjunctivæ or skin, or even from the mucous surfaces. The skin is lemon- or orange-coloured, rarely greenish; pruritus is very frequent. Later, rashes which may be morbilliform, erythematous, or papular may appear. Herpes labialis, which may be hæmorrhagic, is common. In severe cases there may be black vomit.

The urine is highly coloured, nearly always containing albumin and bile, and sometimes casts and red blood-corpuscles. The amount passed is reduced, and the contained albumin may be considerable, and usually persists for seven to ten days, after which a trace only may be found. The leptospira may be demonstrated in the urine from the tenth day onwards, and may persist as long as 100 days; rarely it can be seen in the blood from the twelfth day onwards. Prostration may be extreme. Constipation is the rule; the fæces are pale in colour. The pulse is slow in the later stages, and the blood-pressure low. A polymorphonuclear leucocytosis is present; later there is said to be an increase in the lymphocytes.

After three or four days, in mild cases, the fever subsides by lysis. Slight or even severe febrile relapses are often seen at the beginning of the third week.

The liver, and in rare cases the spleen, may be enlarged; the gall-bladder is distended, and tender on palpation; the lymphatic glands, more especially the inguinal and axillary, are frequently palpable and tender.

Typhoidal, uræmic, and meningeal forms, all of great gravity, have been described. In the meningeal the cerebro-spinal fluid is under pressure, and contains an excess of albumin, and leptospiræ in large numbers.

Epistaxis, hæmaturia, melæna, and hæmoptysis have been noted as complications, and also inflammatory ocular changes, such as iritis and irido-cyclitis. A secondary fever may occur about the seventeenth day without the recurrence of jaundice. The sequelæ are anæmia and debility.

Martin and Pettit recognize the following clinical forms of the disease:

1. Cases with grave icterus.
2. Cases of the true infectious-jaundice type, with febrile recrudescence.
 - (a) Benign catarrhal.
 - (b) Prolonged febrile.
 - (c) Meningeal.
 - (d) With nervous syndrome.
 - (e) Pulmonary.

Diagnosis.—The urine from the fifth to the eighth day is said to give an intense green reaction when one or two drops of acetic acid are added. Early in the disease, if possible before the third day, the blood should be examined under the dark illumination for leptospiræ, and in doubtful cases should be inoculated into guinea-pigs for confirmation. For this purpose 6 c.c. should be injected directly into the peritoneal cavity; citrated blood acts equally well if not kept longer than twenty-four hours. The diagnosis may also be made, probably with more certainty, from the twelfth day of the disease onwards by the injection of the same quantity of catheterized urine. According to Fletcher, the diagnosis is most simply and readily made by direct inoculation of the blood into blood-agar, and subsequent incubation. The disease has to be differentiated from yellow fever, catarrhal jaundice, syphilitic disease of the liver, the icterus of relapsing fever and of malaria. The fever must be distinguished from that of relapsing and of yellow fever, and the leptospira from *Treponema recurrentis*.

In fevers such as typhus and cerebro-spinal fever, and in several others in which relapse may occur, including plague, rat-bite fever, and paratyphoid, especially paratyphoid-B, jaundice may occur as a complication.

An agglutination test for this disease has been devised by Martin, Pettit, and Vaudremer, using a culture of the leptospiræ grown on solid media; it occurs in a titre of 1 in 500, and even as high as 1 in 1,000. The specific agglutinins appear in the serum as early as the sixth, more generally about the tenth day of the illness, and persist for as long as twenty-two months. The centrifugalized deposit of urine rich in these parasites may be utilized in place of a culture, and the diagnosis of infectious jaundice has by these means been placed upon a scientific, if not on a practical basis. The leptospiræ can usually be demonstrated in large numbers in the centrifuged urine, and may be present up to the sixty-sixth day, though they generally disappear on the fortieth. If negative at first, it is recommended that this test should be repeated every second day up to the end of the third week.

An anti-spirochætic serum specific for the *Leptospira icterohæmorrhagiæ* has now been prepared, and by this means the identification of the organism has been made possible.

From the fifteenth day onwards what is known as the immunity reaction may be employed ; for this purpose 1 c.c. of the patient's serum is left in contact for fifteen minutes with several times the lethal dose of the leptospira and injected into a guinea-pig, which will not develop symptoms of the disease, while the control animals will die.

The differentiation of Weil's disease from yellow fever on clinical grounds is usually difficult.

Brown and Davis have shown that the "adhesion phenomenon" is applicable to the diagnosis of Weil's disease as well as of trypanosomiasis. The reaction possesses distinct advantages over agglutination owing to the ease and certainty with which it can be practised. The test consists in allowing the immune serum to interact with the specific leptospira in the presence of a suitable indicator such as bacilli or blood-platelets. Not only can the disease be diagnosed by this method, but it also furnishes a means of differentiating various leptospiræ. It has been shown that *L. icteroides* and *L. icterohæmorrhagiæ* are identical and *L. hebdomadis* quite distinct.

Treatment.—The scientific treatment consists in the administration as soon as possible of a polyvalent antiserum which is prepared from horses injected with cultures of *L. icterohæmorrhagiæ*. This is given intravenously at intervals of several hours for at least four days in succession ; 20 c.c. at least should be given at each injection. For a man of 70 Kg. weight, the dosage is 60 c.c. daily for three to five days. Usually, following this treatment, the temperature begins to fall, but in advanced cases in which uræmic symptoms have supervened the method is of little value. Good results have been claimed from intravenous injection of tartar emetic.

The systematic treatment consists in keeping the patient at rest and flushing out the bowel by means of repeated small doses of calomel, and by intravenous injection of normal saline containing 5–10 per cent. of glucose. Should the nephritic symptoms become severe, intravenous injections of saline or of Ringer's solution, $\frac{1}{2}$ to 1 litre, become necessary. The diet must be liquid and, if vomiting is persistent, should be given as nutrient rectal enemata. For the pruritus accompanying the icterus, tincture of camphor or menthol ointment is recommended.

Failing the provision of commercial anti-leptospiral serum, the serum of patients convalescent from this disease has been injected in daily doses of 30–40 c.c. intramuscularly.

Prophylaxis.—Prophylaxis manifestly consists in sterilizing the faecal and urinary discharges of the patients, and in waging war against the rat, the natural host of the parasite, and carefully guarding against its access to food. Swimming in pools of rivers known to be the source of the disease should be avoided. Noguchi has prepared a vaccine of killed cultures of leptospira which he has used for prophylactic inoculation in Japan.

SEVEN-DAY FEVER

Synonyms.—Nanukayami; Shueki; Sakusku Fever (Japanese); Autumn Fever.

Definition.—A short fever, due to *Leptospira hebdomadis*, occurring epidemically during the summer months, especially in in Japan (Fukuoka), and characterized by sudden invasion, severe headache, pains in the back and limbs, and pyrexia of a peculiar saddle-back, or occasionally of a continued type, lasting from six to seven days and associated with a pulse which is relatively slow in relation to temperature.

History.—Possibly this is one of several fevers included under the term "simple continued fever." Its differential diagnosis from dengue was rendered clear by the discovery in 1918 of the *L. hebdomadis* by Ido, Ito, and Wani.

Geographical distribution.—The home of the disease is Japan, and it is found in China (Shan-si), but possibly occurs also in India and the Dutch East Indies. A disease of dogs in the Malay States has been proved by Fletcher to be produced by a leptospira of the *L. hebdomadis* type.

Etiology.—*L. hebdomadis* resembles *L. icterohæmorrhagicæ* closely, but can be distinguished by serological reactions. The organism is said to be slightly longer by Noguchi, the elementary spirals almost geometrically equidistant. It is present, though in small numbers, in the blood-stream during the pyrexial period, and may be demonstrated by Leishman's stain or by the dark-ground illumination, and is readily cultivated by Noguchi's method. The chief channel of elimination is by way of the kidneys and urine.

The short-eared field-vole (*Microtus montebelloi*) would appear to be the normal host of the leptospira in Japan, and the organism can be detected in the kidneys and urine of 3·3 per cent. of these animals, which can convey the disease by means of their bite. The endemic area of prevalence of seven-day fever corresponds with the distribution of this vole in Japan.

The *microtus*, sometimes termed a field-mouse, in reality a stump-tailed field vole, is common in country districts in Japan. It burrows in the ground and feeds on roots and grain in much the same manner as other small rodents.

The blood of convalescents from seven-day fever contains specific immune and spirochæticidal bodies, and when it is injected, together with a culture of the organism, into the peritoneal cavity of a guinea-pig, a positive Pfeiffer reaction is obtained. Young guinea-pigs are susceptible to inoculation with the blood of patients and with cultures of the leptospira; they may also be infected via the skin or per os.

Symptoms.—The symptoms resemble those of infectious jaundice, and the blood shows a slight leucocytosis. The disease appears to be transmitted by the bite of infected field-mice. The patients are generally workers in the fields and forests.

After a short invasion period the fever comes on briskly, and is accompanied by depression, muscular pains, especially in the calves, conjunctivitis, digestive symptoms, and enlargement of the lymphatic glands. Apparently seven-day fever is a mild disease; it has no mortality, and no distinctive pathological anatomy. The organism can be demonstrated in considerable numbers in the urine of patients after the eighth day, and may persist to the thirty-ninth day. Albuminuria is noted in the early stages.

Differential diagnosis.—The disease is to be distinguished from relapsing fever, infectious jaundice, rat-bite fever, and especially from dengue. There is considerable difficulty in the differentiation from the latter, for many writers have confused the two diseases, and some consider them to be identical, but in view of recent work there can be little ground for adopting this view. The bone-pains and the morbilliform eruption in dengue suffice to distinguish it from seven-day fever.

Treatment.—The disease being generally slight, no specific treatment has been evolved. The fever must be treated on general lines.

NOTE.—In Sumatra various observers have isolated leptospiræ from illnesses of different degrees of severity, including fevers of from one to five days, duration with no jaundice; more severe cases with jaundice; and finally, hæmoglobinuric cases resembling blackwater fever (see p. 46). The organism isolated from mild cases is morphologically identical with *L. icterohæmorrhagiae* and may produce severe symptoms on inoculation into guinea-pigs. Vervoort (1923) has proposed the name of *L. pyrogenes* for organisms isolated from these fevers of short duration.

Fletcher in the Malay States has also isolated leptospiræ from a variety of febrile cases, some resembling dengue, and he has classified the organisms serologically into a number of groups. Owing to the instability of serological reactions, and the fact that primarily non-pathogenic water leptospiræ may be rendered pathogenic so as to produce symptoms of Weil's disease in animals, Baermann and Zuelzer have reached the conclusion that all so-called pathogenic leptospiræ are identical with free-living forms in water. *L. icterohæmorrhagiae* and *L. hebdomadis* may therefore be identical.

CHAPTER VII

YELLOW FEVER

Synonyms.—Typhus Icteroides ; Fiebre Amarilla (Spanish).

Definition.—An acute, specific, febrile disease, occurring epidemically, or as an endemic, within a peculiarly limited geographical area. Though subject to great variations, its typical clinical manifestation may be said to be characterized by a definite course consisting of an initial stage of sthenic nature, rapidly followed by an adynamic condition in which such evidences of blood destruction as black vomit, albuminuria, and hæmatogenous jaundice are liable to occur. One attack generally confers permanent immunity. The virus is transmitted by the domestic mosquito, *Aedes argenteus*, formerly known as *Stegomyia fasciata* (see Plate XII and p. 815) which remains infective for life.

History.—The transmission of yellow fever through a mosquito was foreshadowed by Finlay in 1891. A great advance in our knowledge of this disease was made in 1901 by the brilliant work of Reed, Carroll, and Agramonte. By living among yellow-fever patients in mosquito-protected wards, and surrounded by the excreta and vomit of these patients, themselves remaining free from infection, they proved that the transference of the disease takes place through the bite of the mosquito alone. In 1918 Noguchi described the virus of yellow fever as a small organism, the *Leptospira icteroides*, which, however, is now considered by most authorities to be identical with *L. icterohæmorrhagiæ* (Sellards, Schüffner and Mochtar).

The interest in yellow fever at present centres in W. Africa where it occasions no little concern. As far as information from British and French Colonies is at present available, the pathology of the disease is identical with that of the S. American form; its clinical signs and symptoms, at least in the acute cases, appear to be similar. The virus of the disease can be transmitted to macaque (*Macacus rhesus*) monkeys through many passages by blood inoculation and can be conveyed by the bite of infected *Aedes* from one animal to another almost indefinitely. The mosquito may convey infection even after ninety-one days. Researches on the African disease have entirely failed to substantiate the claim that the *Leptospira icteroides* is the cause of yellow fever.

The discovery of an efficient prophylactic inoculation by Hindle opens up a new chapter in the history of yellow fever.



AËDES (STEGOMYIA) ARGENTEUS, ♀.

Geographical distribution (Map IV).—Of all the important zymotic diseases, yellow fever has the most restricted geographical range. Formerly, from the West Indies, it spread northwards through Mexico to the southern United States, and southwards as far as Monte Video. On the West Coast of South America it was common in Peru, Chile, Colombia, and was known as far north as the Gulf of California, its source of infection in this case being the Isthmus of Panama. At the present time it is only endemic, in the New World, in a few spots in Central and South America and in Brazil. During 1923 the disease was stamped out in Peru.

Yellow fever is endemic apparently on the West Coast of Africa. Its visitations are most irregular. There was an epidemic on the French Ivory Coast in 1922, and one in Southern Nigeria and Gold Coast Colony in 1923. From 1925 to 1927 it was particularly prevalent at the mouth of the Congo, in Nigeria, and has ranged as far north as Liberia and Senegal. In these countries the disease appeared in its most virulent form among Europeans—for little is known as regards its occurrence among the natives, who appear to be immune.

In the past yellow fever has been imported by ships into Portugal, Spain, and Italy, and even to the seaport towns of France and Great Britain, but these small epidemics have been of brief duration.

Epidemiology.—The histories of epidemics show that the virus of yellow fever can be transported from one place to another, and that for its development in epidemic form it requires a mean atmospheric temperature of over 75° F. (24–25° C.). It ceases to spread when the thermometer sinks below this point, and it stops abruptly as an epidemic when the freezing-point is reached. Dampness favours yellow fever; it is therefore most prone to occur and to spread during the rainy season. The favourite haunts of the disease are the sea-coast towns, the banks of rivers, and flat delta country. Rarely does it pass far inland or ascend high ground. There have been, however, exceptions to this general rule, for yellow fever has been found far inland, and at a considerable elevation (São Paulo, Brazil, 2,500 feet). Villages are seldom affected; nor does the disease readily spread if introduced into rural localities. In advancing inland it follows the lines of communication—railways, canals, navigable rivers. Ship epidemics were common occurrences formerly. The ideal haunts of yellow fever are the low-lying, hot, squalid, insanitary districts in the neighbourhood of the wharves and docks of large seaport towns. Yellow fever,

in a sense, is a place disease like malaria. That is to say, if the patient be removed to a hitherto unaffected spot, his attendants and neighbours will not contract the disease unless the spot itself first become infected.

Immunity acquired by prolonged residence or by a previous attack.—A well-established fact about yellow fever is that the natives of, and those who have lived for a long time in, the endemic area are practically immune from the disease; or, if they are attacked, the disease is usually of a very mild type. Relative racial susceptibility may be more a matter of racial opportunity than of colour of skin; the negro from a non-endemic place—Barbados, for example—is just as liable as the European to an attack of yellow fever should he visit an endemic or epidemic area.

Incubation period of an epidemic.—Precise experiments indicate that the incubation period of yellow fever rarely exceeds four or five, with a limit of thirteen days; it may, it is said, be much shorter. The extreme limits are one to fifteen days in the temperate zones, one to thirty days in the tropics. Occasionally it happened that the disease broke out in a ship after she had been several weeks at sea, having had no communication with the land or with another ship in the meantime. This was due to the introduction of infected mosquitoes into the ship before leaving port.

Incubation period preceding epidemic extension.—It has been observed that a period of at least a fortnight elapses between the arrival of a yellow-fever patient in a hitherto uninfected district and the occurrence of the first case of the epidemic he may give rise to. That is to say, that although, as stated above, the incubation period of yellow fever—the period elapsing between the introduction of the virus into the body and the oncoming of fever—is usually only from three to five days, yet a period of at least twelve days must elapse before that virus, after removal from one human body, can be effectively implanted in another human body.

Conditions favouring endemicity.—In order that yellow fever may continue to exist in a community, three factors are necessary—(1) the virus; (2) the vector, *Aedes argenteus*; (3) susceptible human beings living under conditions in which both parasite and man are easily accessible to the mosquito. A short break in this chain is sufficient to eliminate the disease. Yellow fever cannot continue permanently in a community unless the mosquito is present in sufficient numbers. In a population which is to a great extent immune from yellow fever it is obvious that a greater number of infected mosquitoes are necessary to maintain the infection. Instances are on record of the disappearance of the



Geographical Distribution of Yellow Fever.

Black = endemic at present day ; shaded = formerly epidemic or endemic.

MAP IV

disease from towns in South America in which no sanitary work had been done to eliminate the mosquito. The possible explanation would appear to be the lack of enough susceptible persons to continue the life of the virus in man. Unquestionably, in its endemic areas yellow fever exists in a modified or "larval" form among the native children of the community, and the disease may only be recognized as such when it attacks non-immune immigrants.

Etiology.—A great many attempts have been made in the past to discover the germ or virus of yellow fever, and a corresponding number of organisms have been described.

In 1918 Noguchi discovered a leptospira known as *L. icteroides* in Guayaquil. He found that guinea-pigs injected intraperitoneally with a considerable amount (5 c.c. or more) of blood from certain yellow-fever cases developed a train of symptoms comparable to those occurring in man. By the dark-ground illumination method, considerable numbers of this delicate spirochæte, an organism allied to *L. icterohæmorrhagiæ*, were found in the blood, liver, and kidneys; further, he was able to obtain a pure culture of the organism in artificial media and to transmit it through a series of guinea-pigs, and subsequently to recover it in pure culture from their organs.

That the two organisms *L. icteroides* and *L. icterohæmorrhagiæ*, are identical can now scarcely be doubted. Noguchi's leptospira has thus shared the fate of the bacillus described by Sanarelli in yellow fever at the close of the last century.

Adrian Stokes, Bauer and Hudson have now clearly proved that the agent of yellow fever is ultramicroscopic, is filterable in circulating blood and is passed through Berkefeld filters V and W, but is not filterable while developing inside the mosquito. Convalescent serum from severe cases of yellow fever in doses of 0.1 c.c. protects macaque monkeys from further infection with the virus.

Sellards and Hindle have shown that the yellow-fever virus can maintain its vitality when frozen. Liver and blood from an infected monkey were collected in sterile tubes, frozen in a mixture of ice and salt for a period of twelve days and transported from Dakar to London where, when inoculated subcutaneously or intraperitoneally into monkeys, the disease was reproduced.

The optimum temperature for development of the virus within the mosquito is 26° C., the extremes being 18–37° C., or in other words the atmospheric condition of those localities in which yellow fever is endemic. Under natural conditions the percentage of mosquitoes which become infected is very small; possibly this may be explained by the small quantity of blood (0.01 c.c.) imbibed by *Aedes argenteus*, whereas in order to convey the disease with certainty to a non-immune person by direct inoculation 0.1 to 2 c.c. of infected blood are necessary. There is no proof of hereditary transmission in the mosquito. The only mosquito which is proved to be a vector for yellow fever is *Aedes argenteus* and many observations have been made upon

its habits in so far as they affect the etiology of the disease. It has been noted that the female mosquito does not lay eggs until she has fed upon blood, and that these are deposited about three days after feeding. It is generally stated—but this rule is by no means invariable—that before laying her eggs the mosquito is both diurnal and nocturnal in her feeding habits, but that subsequently she becomes strictly nocturnal; therefore it is only the more mature female mosquito that is dangerous as a carrier of yellow fever. For further information on the habits of this mosquito, see p. 815.

The larger African apes and guinea-pigs appear to be immune to inoculation with the virus, but macaque monkeys are extremely susceptible and develop a disease resembling yellow fever: if inoculated with blood during the first three days of the disease, the bite of a single *Aëdes* may suffice to infect a monkey. Infection may be also produced by smearing yellow-fever blood on the unbroken skin. During recent experiments it has been shown that the disease could be conveyed from man to monkeys and also, probably, from monkey to man. The clinical symptoms and pathological changes are the same in monkeys as they are in man.

The observations which have been made upon the etiology of the disease explain certain generally accepted facts: (1) The impunity with which a yellow-fever patient can be visited by a non-immune if outside the endemic area: the mosquitoes in the vicinity are not infective. (2) The danger of visiting the endemic area, especially at night: the mosquitoes are both active and infective. (3) The discrepancy between the incubation period, three to five days, of the disease, and the incubation period, fourteen days and over, of an epidemic: the evolution of the germ in the mosquitoes infected by the original introducing patient demands the space of time indicated by the difference between these two periods. (4) The clinging of yellow-fever infection to ships, buildings, and localities: the persistence of the germ in infected mosquitoes (*Aëdes argenteus*), which are known to be capable of surviving for five months, and probably longer, after feeding on blood. (5) The high atmospheric temperature required for the epidemic extension of yellow fever: such temperature favours the activities and propagation of the mosquito, and is necessary for the evolution of the germ in the mosquito.

Pathology.—Depending probably on hæmoglobin diffused in the liquor sanguinis and tissues, and not on biliary pigment, the olive-yellow colour of the skin is most marked in the dependent parts of the cadaver, especially in those parts which are subjected to pressure. Rigor mortis is pronounced. Petechiæ are common in the skin and serous membranes; more considerable extravasations of blood may be found in the muscles. The brain and meninges are hyperæmic, and may be studded with minute hæmorrhagic effusions; like the other tissues of the body, they may be stained a lighter

or deeper yellow. The cartilages are intensely yellow. The blood in the vessels of the general circulation is not firmly coagulated. The blood-corpuscles appear to be normal, although there can be little doubt that there is in this disease a liberation of hæmoglobin, arising, possibly, from destruction of a proportion of the corpuscles. An important fact, as explaining the liability to passive hæmorrhages, is the existence of a generalized fatty degeneration of the capillaries and smaller blood-vessels. The stomach, as stated, always contains more or less black material, sometimes fluid blood, such as may have been vomited during life, and the stains of black vomit usually are seen about the mouth. The folds of the gastric mucosa are swollen; here and there are arborescent patches of ecchymosis. The small intestine may contain a dark, acid material similar to that in the stomach, and doubtless coming from the same source. Like that of the stomach, the mucous membrane of the intestine shows patchy arborescent injection.

As compared with other fevers, in yellow fever the liver is characteristically affected. If death has occurred at the later stages, this organ is usually somewhat friable, and, from profound fatty changes in the cells, presents a yellowish colour, which has been compared to that of boxwood. Throughout the gland the cells—particularly those about the periphery of the lobules—on microscopic examination are found to be necrotic and studded with extravasated blood. The nuclei in some instances, as well as the protoplasm of the cells, show fatty changes; the latter may be completely disintegrated. In the great majority of cases this fatty degeneration is well marked. It is not confined to the liver; every organ of the body is more or less affected in the same way. The toxin of yellow fever has an especial affinity for liver-cells.

The spleen is not characteristically affected, but the kidneys show signs of parenchymatous nephritis. Hæmorrhagic foci under the capsule and in the cortex are common. The renal epithelium shows cloudy swelling passing on to fatty degeneration and desquamation, which affects the tubules more than the glomeruli. The tubules, here and there, are filled with infarcts, either of an albuminoid material or of debris of desquamated epithelium, corresponding with the numerous casts which can be discovered in the albuminous urine. Hoffman regards the presence of lime-casts in the convoluted tubules as distinctive of yellow fever, and similar changes are found in the kidneys of the experimentally produced disease in guinea-pigs. No essential differences between the pathology of South American and West African yellow fever have been noted. Seidelin, Turnbull, and recently Klotz and Simpson, have shown that one of the characteristic features in the pathology of yellow fever is the hyperplasia of the endothelial cells of the sinuses of the liver and similar changes in the spleen. In this particular the pathology of yellow fever resembles that of the typhus group of diseases.

Symptoms.—There is the same variety in the initial symptoms of yellow fever as in other specific fevers. There may be sudden rigor occurring in the midst of apparent health; there may be only slight chills; or there may be a period of premonitory malaise leading up to the more pronounced symptoms. When fairly started, the procession of events is rapid. The incubation period is from three to six days.

Roughly speaking, and provided there are no complications,

What with pain and febrile distress the patient rapidly passes into a very miserable condition. He is restless and continually tossing about.

At first the pulse ranges from 100 to 120, and is full and strong ; but as the disease progresses the pulse loses its sthenic character, gradually falling in force and frequency until, at the "period of calm," it becomes remarkably slow and compressible, beating perhaps only 30 or 40 times per minute. This fact is of particular value in diagnosis, and is known as *Faget's sign*—that is, a falling pulse-rate with a constant temperature, or a constant pulse-rate with a rising temperature.

At the outset the tongue is not very dirty, but it soon acquires a white coating on the dorsum, the edges remaining clean. It is not so swollen and flabby as in malarial fever ; on the contrary, it is rather small and pointed throughout the disease. This is regarded as an important diagnostic mark ; taken along with the progressive diminution in the strength and frequency of the pulse and the peculiar behaviour of the temperature, it is nearly conclusive as to the disease being yellow fever. Later, the tongue dries and, at the same time, thirst becomes intolerable. The palate is congested and swollen ; the gums may also swell and bleed.

The congested appearance of the face at the onset of the disease tends to subside ; so that by the time the asthenic stage is reached the features may have become small, the eyes sunken, and the eyelids discoloured by ecchymoses.

In some cases the skin is hot and dry throughout ; in others it may be bedewed with perspiration from time to time ; or the sweating may be constant, especially if collapse sets in.

By the third day the scleræ assume a yellowish tinge, and very often the skin acquires the yellow colour from which the disease derives its name. It must not be understood, however, that every case presents this colour of skin ; in some it is entirely absent, but if carefully looked for there is always some yellowness of the scleræ to be discovered. The yellow tinging of the skin generally shows about the end of the first stage, deepening in intensity as the case advances, and remaining apparent for a considerable time after convalescence has become established. It ranges in depth from a light saffron tint to a deep mahogany brown. In fatal cases it is always present—not necessarily during life, but invariably after death. The skin in bad cases is said to emit a peculiar odour like gun-washings, or, as Jackson puts it, like the smell of a fish-market.

Petechial, erythematous, papular, and other eruptions may show themselves in different cases ; but in yellow fever there is no

characteristic eruption, unless it be an erythematous congestion of scrotum or vulva, which occurs in a proportion of cases and is described as diagnostic. Bleeding from the gums is said to be characteristic.

An important feature, from the diagnostic as well as from the prognostic point of view, is the appearance, in some cases almost from the outset of the disease, of albumin in the urine, together with a tendency to suppression. In mild cases these features may be little marked; but in severe cases, particularly during the stage of depression, the urine may fall to a few ounces, and be loaded with albumin to the extent of one-half or even two-thirds (usually about 2 gm. of albumin per litre). The more pronounced these symptoms, the graver is the prognosis. It has been noted that the amount of albumin increases as the temperature falls. Urea (even during the incubation period) and uric acid are very much diminished, the former in severe cases falling to 1.5 gm. to the litre. The urine is almost invariably acid, depositing granular casts, and giving spectroscopic evidence of hæmoglobin. Bile-pigments show themselves towards the end of the disease; their appearance is regarded as a favourable omen. Hæmorrhage from kidneys or urinary tract is not uncommon.

Insomnia is usual, but if it occurs before the third day the prognosis is said to be grave. Delirium may occur, but is not an invariable feature. Usually, after the initial stage of restlessness and acute suffering, the patient becomes torpid, and perhaps taciturn. In bad cases coma, subsultus, etc., may gradually supervene, the temperature rising as death approaches, and even after death. A well-marked *tache* is present on the forehead as well as on other parts of the body.

At the outset the bowels are confined. In the second stage, diarrhoea, perhaps of black material resembling the vomit (*see below*), may supervene; or there may be actual hæmorrhage of bright-red blood from the bowel.

Nausea and vomiting are more common than in other fevers. The well-known *black vomit*—always a grave symptom, but fortunately not by any means an invariable one—forms one of the most striking features of this disease. In the earlier stages of the fever, vomiting of bilious matters is a common occurrence. This may subside or, after a time, give place to a coffee-grounds vomit which seems to gush up without straining or effort on the patient's part, and which gradually deepens in colour until it becomes uniformly black. On microscopical examination the vomited material is found to consist of broken-down blood-corpuscles and

altered hæmoglobin suspended in a yellowish mucoid fluid. This material is, doubtless, in the main derived from blood transuded through the walls of the capillaries of the mucous membrane of the stomach. It is intensely acid. Though the black vomit may not always be seen in fatal cases during life, the material is invariably found in the stomach on post-mortem examination.

Sometimes pure blood is thrown up from the stomach ; similar passive hæmorrhages may take place from almost any part of the body—from eyes, ears, nose, mouth, bladder, uterus and so on. "Everything is congested at the outset, everything bleeds at the end," is a well-known adage in regard to this disease.

Death may occur during the early acute stage, being preceded by a rapid rise of temperature. The majority of deaths occur on the fifth and sixth days ; the end seldom comes before the third or after the eleventh day. It is generally preceded by a rapid fall of temperature.

In mild cases the "period of calm," which sets in after the subsidence of the initial fever, may last for several days before convalescence is established. In such cases recovery, once begun, is usually rapid ; in a week from the beginning of the disease the patient may be about again. In severe cases, however, the period of calm is followed by a third stage, the stage of reaction, in which the temperature again rises, though not to so high a point as in the initial fever, and a sort of remitting fever of an adynamic type keeps on for several days or weeks. This secondary fever is more prolonged if there is any complication, such as abscess, boils, parotitis, buboes, or hepatitis. The icterus is now very pronounced ; black vomit may recur, or appear for the first time ; perhaps a profuse diarrhœa ends in collapse ; or the urine may be suppressed, stupor, coma, and other nervous symptoms ensuing, and very often ending in death. In other instances the secondary fever terminates in a crisis of sweating and a prolonged convalescence.

Relapses are rare, and when they do occur are dangerous. The immunity produced by one attack of yellow fever is usually permanent, as permanent as that produced by smallpox or measles.

As a rule, there is no anæmia, but there is a slight leucocytosis early in the disease, soon followed by a leucopenia ; the polymorphonuclear cells predominate.

Diagnosis.—Practically the only diseases with which severe yellow fever is likely to be confounded are *bilious remittent*, *infectious jaundice* (Weil's disease), and *blackwater fever*. The difficulties of diagnosis on clinical grounds are often great, particularly in the

earlier cases of an epidemic. When several deaths, preceded by fever and black vomit, have occurred within a limited area and in quick succession, a suspicion of yellow fever becomes a certainty. There is no clinical feature, so far as is known, which would distinguish a mild attack of yellow fever from an ordinary febricula, nor any pathognomonic clinical sign that would absolutely distinguish a malarial remittent from yellow fever and from infectious jaundice. *Dengue* is probably one of the most difficult diseases to differentiate from mild yellow fever. The facies, orbital pains, and backache are similar to those of dengue, but the appearance of the characteristic eruption of the latter disease on the fourth day should settle the diagnosis in any doubtful isolated case. Probabilities must be weighed in diagnosis when it is based on clinical grounds alone. The only reliable guides, as between malarial and yellow fever, are the discovery of the malaria parasite and the characteristic pigment and leucocytic variation in the one, and the determination of their absence in the other; and, when cases come to the post-mortem table, the presence of pigment in the viscera in the former, and of extensive fatty degeneration of the liver-cells in the latter. Occasionally the two diseases may coexist.

Prognosis and mortality.—Prolonged initial rigors, algidity, convulsions, suppression of urine, coma, hæmorrhages, are all unfavourable symptoms. The prognosis is good if the temperature during the initial fever does not exceed 103° to 105° F. It is better for women (although, if pregnant, abortion is almost invariable) and children than for men; better for old residents than for newcomers; worst of all for the intemperate. According to a table given by Sternberg, of 269 carefully observed cases there were no deaths in 44 in which the temperature did not rise over 103° ; in 22 cases in which the thermometer rose over 106° there were no recoveries. The mean mortality in the whole 269 cases was 27.7 per cent. In some epidemics it has risen as high as 50 or even 80 per cent. of those attacked, but the foregoing may be taken as a fairly representative mortality in yellow fever among the unacclimatized—something between 25 and 30 per cent. Among the permanent inhabitants of the endemic districts the case-mortality is very much lower—7 to 10 per cent. During epidemics, abortive and ambulatory cases occur; in these, icterus and other characteristic symptoms are often absent. Such cases may be hard to diagnose from febricula or mild malarial attacks. In them the mortality is nil. Some epidemics are particularly mild; in others the majority of the patients die. In the same epidemic the cases may vary in severity from time to time. In children the mortality is insignificant.

Treatment.—Formerly a much more active treatment than that in vogue at the present day was the fashion for yellow fever. It is now recognized that, as with most specific fevers, the treatment is more a matter of nursing than of drugs. Once in bed, the patient should not be allowed to get up.

Experience has shown that a smart purgative at the very onset of the disease is beneficial. With many, castor oil is the favourite drug, but to be of service it has to be given in very large doses—2 oz. or more. Others use calomel, or calomel combined with quinine. Others, again, prefer a saline.

Hot mustard pediluvia, frequently repeated during the first twenty-four hours, the patient and bath being enveloped in a blanket, are much in favour. They are said to relieve the cerebral congestion and the intense headache. Very hot baths, with subsequent blanketing and sinapisms to the epigastrium, are also said to have a similarly favourable influence on the congestion of the stomach, which is, undoubtedly, another constant feature of the disease. For high fever, antipyretic drugs, cold baths, iced injections, cold sponging, and the like may be carefully employed. In view of the asthenic nature of the disease, the less depressing measures should be preferred.

Vomiting may be treated with sinapisms and ice pills, or with small doses of cocaine. Morphia is dangerous and must be avoided. For black vomit, frequently repeated doses of perchloride of iron, ergotine injections, acetate of lead, and other styptics have been recommended. A distinct advance in the treatment of the hepatic conditions is the administration of glucose, given in drachm doses by the mouth, whenever feasible, or when nausea is present, in 5-per-cent. solution intravenously (10 oz.). Le Fanu reports good results from this line of treatment originally suggested by Balfour. For restlessness, phenacetin or antipyrin is used. When the skin is dry, the urine scanty, and the loins ache excessively, Sternberg recommends pilocarpine.

After the fourth or fifth day the flagging circulation demands stimulants of some sort. Iced champagne, hock, or teaspoonful doses of brandy given every half-hour may tide the patient over the period of collapse. Great care, however, should be exercised in the use of these things; if they seem to increase the vomiting and the irritability of the stomach they must be stopped at once.

Free ingestion of water tends to obviate the failure of renal function, which is the usual form of death.

The feeding is an important matter. So long as there is fever the patient has no appetite; during this time—that is, for the

first two or three days—he is better without food. When the fever subsides appetite may return, and a craving for nourishment becomes more or less urgent; the greatest care, however, must be exercised about gratifying this untimely appetite. Only the blandest foods, and these only in very small quantities, should be allowed—such as spoonfuls of iced milk or chicken tea. Gradually the quantities may be increased; but even when convalescence is established solid food must be partaken of very sparingly, and it must be of the simplest and most digestible description. Indiscretion in eating is a fruitful cause of relapse in yellow fever; and it must be borne in mind that in this disease relapse is exceedingly dangerous. Nutrition may be aided by nutrient enemata.

The *Sternberg treatment* is directed principally to counteracting the hyperacidity of the gastric and intestinal contents—always a marked feature of yellow fever. The prescription is 150 gr. of sodium bicarbonate and $\frac{1}{3}$ gr. of mercury perchloride in a quart of water; of this $1\frac{1}{2}$ oz. is given every hour.

Prophylaxis.—It is the duty of sanitary authorities in tropical countries, so far as possible, to free from mosquitoes the areas over which they have charge. Although complete extermination is not to be expected, relative extermination of mosquitoes is worth attempting, and certainly much can be attained in this direction by the vigorous use of the now well-known measures. In Havana, by such means, in a very few months the number of mosquitoes was reduced 90 per cent., with a corresponding gain to the community in the diminution of mosquito-conveyed disease. The same has happened in Panama, Rio, and elsewhere.

During epidemic visitations or during exacerbations of endemic yellow fever, non-immunes should, if possible, immediately quit the implicated locality. Above all, the slums and low-lying districts of the town should be shunned. These places should not even be visited; or, if visits have to be made to them, they should be as brief as possible, and not made after sundown. The susceptible should not sleep in the lower stories of houses, and should pay great attention to general health, carefully avoiding all causes of physiological depression or disturbance. Sailors must not be allowed on shore.

All water-tanks and cisterns must be effectually screened by fine-meshed metallic gauze against *Aedes argenteus*; all puddles and stagnant water abolished; all cases of any kind of fever, no matter how mild they may be or what their nature, must be reported at once to the central sanitary authorities, who should have full powers promptly to screen or otherwise deal with them

and the houses in which they originated. The general use of mosquito-nets must be insisted upon.

Any delay in recognizing the earliest cases of a threatened epidemic is, as shown by experience in New Orleans, most dangerous, leading, as it may, to the rapid multiplication of infected centres.

Ships should not be allowed to clear from infected ports, nor to enter non-infected ports, during the warm season, without adequate inspection. Steamers trading on the Amazon have now been made relatively mosquito-proof by means of wire-gauze netting fitted to the windows and doors.

Should the disease appear in a locality which is not habitually a yellow-fever centre, and of which the population is small, an economical plan of dealing with the threatened danger is for the authorities promptly to remove the entire population of the neighbourhood, with the exception of the insusceptible and those in attendance on the sick, and to place the deported population, before dispersion, in a thirteen days' quarantine camp.

In the event of yellow fever breaking out in the crew of a man-of-war, the cases, if possible, should be sent ashore, and the ship hurried north or south into cold weather, any mosquitoes which may have found their way on board being at once destroyed.

In the case of the appearance of yellow fever in a large town, the method which was so successfully employed by the late Surgeon-General Gorgas must be adopted. Funds and authority must be obtained at once. An efficient and adequate sanitary staff must be promptly organized and instructed in their duties. Cases of every kind of fever as well as cases of yellow fever should be immediately reported, and the patients promptly protected from mosquito-bite by wire screens. At the same time the systematic destruction of mosquitoes in their breeding-places and in the patients' and neighbouring houses must be rigidly enforced. The infected houses should be carefully sealed up by pasting paper over all the doors, windows, ventilators, chimneys, and cracks, and the fumes of pyrethrum or of burning sulphur—2 lb. per 1,000 cubic feet of space—or other insecticide employed to stupefy the insects, which should afterwards be swept up and burned.

Guiteras has shown, in a practical manner, that yellow-fever patients may be admitted to the wards of a general hospital or be nursed in private houses with impunity, provided they are protected by effective mosquito-netting from mosquito-bite during the first three or four days of their illness.

Prophylactic inoculation.—Recent reports from West Africa indicate that protection can be conveyed to non-immunes by inoculation of the convalescent serum of those who have recovered from an attack of yellow fever, while Hindle has produced what appears to be an efficient prophylactic inoculation against the virus of yellow fever which is protective for macaque monkeys. The vaccine consists of an emulsion (of liver and spleen of an inoculated monkey which has succumbed to yellow fever) in glycerine, 600 c.c.; 5-per-cent phenol 100 c.c.; distilled water 300 c.c. This emulsion, after being filtered, is kept at room-temperature for seven days and then placed in the ice-chest. Of this extract, 1 c.c. inoculated subcutaneously, produces a primary fleeting reaction and is then followed by a high degree of immunity. In uninoculated monkeys it is found that the injection of 0.0001 gm. of infected liver is a fatal dose, but subsequent to protection with the vaccine, monkeys are able to withstand 1 gm. of yellow-fever liver virus with impunity.

CHAPTER VIII

DENGUE AND PHLEBOTOMUS FEVER

I. DENGUE

Synonyms.—Dandy fever; Breakbone Fever, Chapenonada (Philippines), Seven-day Fever (Rogers).

Definition.—A specific fever conveyed by *Aedes argenteus* (*Stegomyia fasciata*) and, possibly, other mosquitoes, occurring usually as a rapidly spreading epidemic. Throughout the febrile stages, and often subsequently, severe rheumatic-like pains are a prominent symptom. The disease in its active form lasts about a week, and is attended with little, if any, mortality.

Geographical distribution and mode of spread.—Dengue is apt to occur in epidemics, and has appeared in Syria, Asia Minor, on the Ægean shores of Greece and Turkey, in North Queensland, in Charleston and Philadelphia in the United States, and as far south as São Paulo in Brazil. It is endemic in the West Indies, Fiji, Samoa, and other Pacific islands.

Epidemiology and endemology.—The characteristic of dengue fever is that it is apt to recur at intervals of years, sometimes in pandemic waves, during which, it may be, three-fourths of the population are attacked. The epidemic may last for one season or may be spread over several years. Between these epidemics cases occur sporadically, by which means the virus is maintained, and forms the nidus of infection for a new epidemic, but owing to their mild nature they are frequently not recognized. In its pandemic form the disease often appears at a considerable distance beyond its usual confines, and may even ascend mountains to a height of 5,000 feet. The epidemiology appears to be dependent more upon conditions which are suited to the particular mosquito that conveys the disease, than upon those which affect man.

When dengue spreads beyond its ordinary tropical limits, as for example in the epidemics of Philadelphia and Asia Minor, the extension occurs only during the hottest part of the year—in the late summer and early autumn.

Epidemics occur generally after the rainy season and, in the

Pacific islands, at any rate, the disease appears to have a seasonal incidence during June, July, and August.

It would appear that dengue, like yellow fever, prefers the coast-line, and the deltas and valleys of great rivers, to the interior of continents.

Etiology.—The organism of dengue has not yet been recognized. Graham, in Beirut, Syria, first suggested that the disease was transmitted by a mosquito, *Culex fatigans*.

More recently, by a series of well-conceived and carefully-carried-out experiments, Cleland, Bradley, and MacDonald in Australia have proved that the virus of dengue is conveyed by *Aedes argenteus* (*Stegomyia*), and not by *Culex fatigans*. By subinoculation from one individual to another they transmitted the disease for four generations, and showed that the virus is present in the blood from the second to the fourteenth day of the disease. Recent experiments by Siler have confirmed this work. He found that the blood in dengue is infective to the mosquito for eighteen hours before onset to the end of the third day of the illness. The mosquito, *A. argenteus*, itself does not become infective for eleven to fourteen days, but then remains so for the rest of its life. Passage of the virus through man to the mosquito fails to attenuate or increase it.

Pathology.—On account of the low mortality, post-mortem records are few. In the autopsies recorded, localized pulmonary and intracranial inflammation were the special features. Serous effusions in the neighbourhood of joints and inflammation of the crucial ligament of the knee have also been noted.

Symptoms.—The *incubation period* seems to be somewhat variable, generally from five to nine days, though sometimes it appears to be less. The course of the disease may be divided into three periods: the stage of invasion, lasting two to three days; the stage of remission, lasting twelve hours to three days; the terminal fever and eruption.

Stage of invasion.—An attack of dengue may be preceded for a few hours by a feeling of malaise or, perhaps, by painful rheumatic-like twinges in a limb, toe, finger, or joint. Usually it sets in quite suddenly. Sometimes the fever is ushered in by a feeling of chilliness or even by a smart rigor; sometimes a deep flushing of the face is the first sign of the disease. However introduced, the fever rapidly increases. The head and eyeballs ache excessively, and some limb or joint, or even the whole body, is racked with peculiar stiff, rheumatic-like pains, which, as the patient soon discovers, are very much aggravated by movement.

The loins are the seat of great discomfort, amounting in some cases to actual pain; the face—particularly the lower part of the forehead, round the eyes, and over the malar bones—may become suffused a deep purple; and often the skin over part or the whole of the body, and all visible mucous surfaces, are more or less flushed, those of the mouth and throat being sore from congestion and perhaps from small superficial erosions. The eyes are usually much injected; very often the whole face is bloated and swollen. This congested, hypersensitive, and erythematous state of the skin constitutes the so-called prodromal eruption. There may be a *tache cérébrale*.

These symptoms becoming in severe cases rapidly intensified, the patient, in a few hours, is completely prostrated. His pulse has risen to 120° or over; his temperature to 103° F. (Chart 11), in some cases to 105°, or even to 106°. He is unable to move owing to the intense headache, the severe pain in limbs and loins, and the profound sense of febrile prostration. From time to time the skin may be moistened by an

abortive perspiration, but for the most part it is hot and dry. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow. In this condition the patient may continue from one to three or four days, the fever declining somewhat after the first day.

In a proportion of cases, and particularly in certain epidemics, crisis does not occur, the fever slowly declining during a period of three or four days.

Stage of remission.—When the second stage is established and the thermometer has sunk to normal, the patient is sufficiently well to leave his bed and even to attend to business. The tongue clears, and the appetite and sense of well-being return to some extent.

Terminal fever and eruption.—The state of comparatively good health continues to the fourth, fifth, sixth or even to the

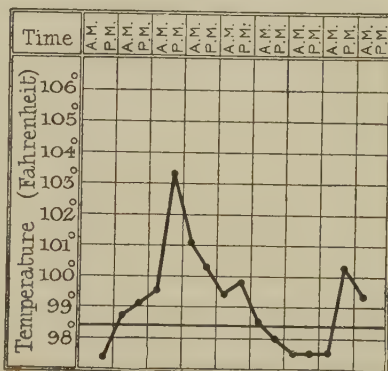


Chart 11.—Dengue. (After Cleland and Bradley.)

seventh day, counting from the onset of the illness. Then there is generally a return of fever, slight in most cases, more severe in others. With the recurrence of the fever an eruption of a rubeolar character, consisting of dark, dusky spots, appears. The pains likewise return, perhaps in more than their original severity. Though the fever subsides in a few hours, the eruption, at times very evanescent, may keep out for two or three days longer, to be followed very generally by an imperfect furfuraceous desquamation.

Characters of the eruption.—The terminal eruption of dengue possesses very definite characters. It is absent in a very few cases, but in many, being slight, it is overlooked. Usually it commences on the palms and backs of the hands, extending for a short distance up the forearms. It quickly extends, and is best seen on the back, chest, upper arms (Plate XIII), and thighs. Here it appears at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots, $\frac{1}{8}$ to $\frac{1}{2}$ in. in diameter, thickly scattered over the surface, each spot being isolated and surrounded by sound skin. There may be a general coalescence of spots, isolating here and there patches of sound skin; in this case the islands of sound skin give rise, at first sight, to the impression that they constitute the eruption—a pale eruption, as it were, on a scarlet ground, giving an appearance of a condition “midway between scarlet fever and measles.” The spots disappear on pressure, and never, or rarely, become petechial. They fade in the order in which they appear—first on the wrist and hands; then on the neck, face, thighs, and body; last, on the legs and feet, but may still be visible for three weeks after recovery from the fever.

Desquamation may go on for two or three weeks. In many it is trifling in amount; for the most part it is furfuraceous.

At this stage the characteristic slowing of the pulse, which may fall as low as 44 per minute, and the leucopenia, which may fall as low as 1,200 leucocytes, are noted; the latter is due to a marked decrease of the polymorphonuclear cells, which may be reduced to 40 per cent., and to a relative increase of the lymphocytes.

Rheumatoid pains persist for some time after convalescence has been established. They are usually worst on getting out of bed in the morning and on moving the affected part after it has been at rest for some time; they are relieved somewhat by rest and warmth. In some cases a periarthrits of the knee- or ankle-joint which may cause considerable disablement does not clear up for several months.

Convalescence may be very much delayed by anorexia, general



DENGUE RASH.

(Partly after Cleland and Bradley.)

PLATE XII

debility, mental depression, sleeplessness, evanescent feverish attacks, boils, urticarial, lichenoid, and papular eruptions.

In Europeans an attack of dengue very often leads to a condition of debility, necessitating temporary change of climate, or even return to Europe.

Variability of epidemic type.—Judging from the published descriptions, there is considerable variety in the symptoms of this disease in different places and in different epidemics. Some authors mention swelling and redness of one or more joints as a common and prominent symptom; others refer to metastasis of the pains, enlargement of submaxillary glands, orchitis, mental depression, hæmorrhages, and so forth, as being frequently present. However this may be, the essential symptoms in well-marked cases are the same practically everywhere and in all epidemics, viz. suddenness of the rise of temperature, an initial stage of skin congestion, limb and joint pains, and a terminal rubeoloid eruption.

Relapses are not uncommon in dengue, and second and even third attacks during the same epidemic have been recorded. As a rule, however, susceptibility to the disease is exhausted by one attack.

Mortality.—In uncomplicated dengue the mortality may be said to be almost nil (0·1 per cent., Hare).

Diagnosis.—Dengue must not be confounded with yellow fever, rötheln, scarlatina, measles, syphilitic roseola, influenza, cerebro-spinal meningitis, typhus, hæmorrhagic smallpox, enteric, phlebotomus fever, seven-day fever, rheumatic or malarial fever. A knowledge of the distinctive features of these diseases, and the fact that dengue is attended with a rash and with articular pains, and that it occurs in great and rapidly spreading epidemics, should prevent any serious error in diagnosis.

Treatment.—Were it possible to secure perfect isolation and immunity from mosquito-bite for the individual during an epidemic of dengue, doubtless he would escape the disease. Even comparative isolation is attended with diminished liability.

Like the allied fevers, dengue runs a definite course; therefore it is useless to attempt to cut it short. The patient should go to bed as soon as he feels ill, and should keep his room till the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, light liquid diet, rest, and the avoidance of chill conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture, with aconite, may be prescribed with advantage. If the pains be severe and the fever high, anti-

pyrin, or phenacetin, belladonna, or vinum colchici (15 min. t.d.s.), give great relief. Cold applications to the head are comforting. If the temperature rises to 105° F. or over, cold sponging or the cold bath ought to be had recourse to. If the pains continue very distressing, a hypodermic injection of a minute dose ($\frac{1}{10}$ gr.) of morphia will afford welcome relief and do no harm. Purgatives and emetics should be avoided unless pronounced constipation, or a history of surfeit, urgently demands their exhibition. The pain caused by the muscular movements entailed by the efficient action of purgatives more than counterbalances any advantage the latter might otherwise bring. Wine in the early stage is not advisable. Freshly-made lemonade, or iced water, will be found an acceptable drink during the fever.

For the pains experienced during convalescence, rubbing with opium or belladonna liniment, gentle massage, electricity, salicylates, small doses of iodide of potassium, have been advocated. Debility, or anorexia, indicates tonics such as quinine, strychnine, mineral acids, or vegetable bitters, and change of air.

Prophylaxis is the same as for yellow fever and for other mosquito-borne diseases, and is directed against infected mosquitoes.

II. PHLEBOTOMUS FEVER

Synonyms.—Papataci Fever; Three-day Fever; Sandfly Fever; "Dog Disease."

Definition.—A specific fever of short duration and no mortality, caused by a germ introduced by the bite of the sandfly (*Phlebotomus*).

History.—This disease has been recognized clinically for upwards of a century, and described under a variety of local names; but its definite relation to its transmitting agent, although suspected by McCarrison in Chitral in 1903, was not established till 1908, when Doerr published his observations, since confirmed by Kilroy, on the infectivity of the blood in this form of fever and the rôle of the sandfly as transmitter. Whittingham has described minutely the various stages in the life-history of the phlebotomus, and has succeeded in rearing these insects in captivity.

Geographical and seasonal distribution.—The range of phlebotomus fever is probably coextensive with that of the insect transmitter. In the tropics it may break out at any time as an epidemic amongst new arrivals; in the subtropics it occurs only or principally during the summer and early autumn. Natives of the endemic area appear to be immune. Where the phlebotomus is absent, e.g. Bermuda, this fever is not found. In some phlebotomus-haunted places as many as 50 per cent. of new-comers are

attacked. This fever was much in evidence during the Great War, in Gallipoli, Salonika, the Ægean Islands, Egypt, Palestine, Syria, Mesopotamia, and India, but there is no record of its occurrence among troops in East Africa. Widely distributed in Africa and Asia, sandfly fever is found in the Caucasus, Chitral, and the Himalayas, up to a height of 4,000 feet. In the New World it has recently been found in northern Argentina.

Etiology.—The germ resides in the patient's blood during the first two days of the fever. It is ultramicroscopic, passing through filters which arrest *Brucella melitensis*. According to Doerr, the virus is transmitted hereditarily through the egg and larva of phlebotomus to the imago; this, however, has not been firmly established. A short sharp fever has been produced in monkeys after intravenous injection of sandfly-fever blood. In Egypt, it is said, a similar fever exists in cattle which may possibly act as reservoirs of infection to man. According to Whittingham, the virus may survive the winter, either free in the soil, or within the bodies of phlebotomus larvæ which inhabit such sites as moist soil and porous walls. The larva extracts the virus in feeding upon the fæces of the adult fly.

Representatives of the genus *Phlebotomus* are to be found in most tropical and subtropical countries. The various species are usually designated "sandflies." They are exceedingly minute, very delicate yellowish, greyish, or brownish, somewhat slenderly-built insects that bite principally during the night and that can pass easily through the meshes of an ordinary mosquito-net. The powers of flight are feeble; more usually the insects progress by a series of short skips.

P. papatasi, the species on which Doerr's observations were made (hence one of the names for the disease, papataci fever), lays about forty eggs, selecting for the purpose damp localities such as the walls of cellars, of latrines, cesspools, crevices in walls, caves, and embankments. The cycle of egg, larva, and imago takes about one month in warm and upwards of two months in cooler weather (see p. 817).

There has been much confusion in the nomenclature of the various species of *Phlebotomus*, and it has not been determined which of them, other than *P. papatasi*, convey the infection. The insect can transmit the infection after an incubation period of six days.

Pathology.—Dengue, and phlebotomus fever have several important points in common, a circumstance suggestive of the possibility of a common or, at all events, a similar origin. Each is transmitted by an insect; their

germs occur in the blood-stream and are filterable; they are diseases of warm climates only; and clinically, they are characterized by a short incubation period and a brief and rapidly developed fever which is usually associated with relatively slow pulse and leucopenia, and relative decrease of the polynuclears. It would be interesting to ascertain if these diseases are mutually protective.

Symptoms.—The bites of the sandfly occasion a considerable amount of irritation, resulting in hyperæmia and even in œdema. After an incubation period of from four to seven days, with or without a prodromal stage, the fever is ushered in suddenly by slight or more severe rigor. The face becomes flushed and swollen, frontal headache is intense, and there is usually severe general aching and stiffness in the back of the neck. Pain at the back of the eyes, accentuated by pressure on the globes or by the least movement of the head, is characteristic. Supraorbital headache is also quite common. There are influenzal pains in the back and legs and general stiffness of the muscles—more rarely the pain is referred to the epigastrium. The patient is drowsy, but suffers from insomnia. The conjunctivæ are so injected that they have been likened to those of a mastiff. The tongue has a central fur. The fauces and palate are often congested, and are studded with small vesicles. In from twenty-four to thirty-six hours the temperature has reached $103-4^{\circ}$ F. (Chart 12). It keeps about this point for a day longer, and then begins to fall, with or without epistaxis, vomiting, sweating, diarrhœa, reaching the normal about the end of the third or beginning of the fourth day. The patient continues debilitated, especially mentally, for a week or two longer. According to Lambert, the name “three-day fever,” as applied to the disease, is quite misleading, since the pyrexial period may occasionally vary from two to eight days.

The blood picture shows a slight leucopenia without serious alteration in the number of mononuclears. The pulse-rate is relatively slow.

No serious complications occur, but in some years diarrhœa, in other years pharyngitis, is a feature of the epidemic. An attack would seem to confer a certain amount of immunity, though second attacks are by no means uncommon, but are milder than the primary ones.

There are no important sequelæ, save that the debility which ensues in some individuals is quite out of proportion to the intensity and duration of the initial attack. The mortality is nil.

Diagnosis.—It is extremely difficult in the early stages to distinguish this fever on clinical grounds from malaria (especially

subtertian), from paratyphoid, dengue, typhus, and influenza. In typhus the greater hebetude, and in influenza the respiratory catarrh, must be taken into consideration.

Treatment.—The most valuable drug in the treatment of sandfly fever is opium; 30 drops of the liquor opii sedativus may be given at the onset. It greatly relieves the headache. Quinine is useless. Tincture of iodine should be applied to the bite.

Prophylaxis.—As it would appear that phlebotomus fever is a

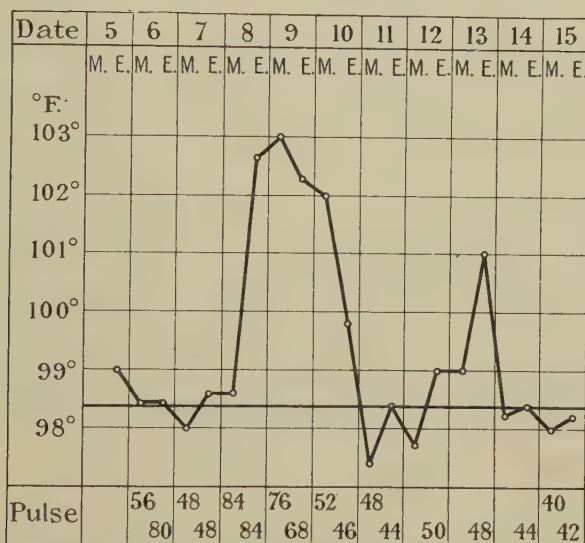


Chart 12.—Phlebotomus fever showing prodromal period, typical attack, recrudescence and bradycardia. (*Lambert. Jl. Roy. Nav. Med. Ser.*)

disease of locality, houses and places believed to be infected should be avoided and, where possible, disinfected.

With a view to diminishing the local sandfly pest, all rubbish should be burned or otherwise got rid of; ruinous walls demolished, the cracks in walls filled in with tar or mortar, latrines smoked with sulphur fumes and put into sanitary condition, and dark damp places dried, whitewashed, and ventilated. No gardens or cultivated ground should be permitted in the immediate vicinity of buildings, and creepers should not be allowed to grow on barrack walls. The adult flies can be killed in numbers by "swatting." By these and similar measures much can be done to control the infection. Unfortunately, a mosquito-net having a mesh

sufficiently small (i.e. 45 holes to the inch) to keep out sandflies is intolerable to a white man in a hot climate. As the phlebotomus does not fly higher than 10 ft., the removal of inmates to an upper story is a very effectual preventive measure. It is said that a lump of camphor placed in the bed repels the insects. Of the repellent ointments in use for application to the skin, the following is considered the most efficacious (Balfour):

R̄ Ol. anisi	} āā ℥iii.
Ol. eucalypti	
Ol. terebinth.	
Lanolini	℥i.

Choyce recommends 5-per-cent. thymol made up with firm wax into a candle and rubbed into the skin, where it forms an oleaginous covering, as an excellent general prophylactic measure

To reduce the incidence of sandfly-bites general measures should be instituted. Shorts should not be worn after sundown, wrists and ankles should be smeared either with the above ointment, or with "vermijelli," or oil of citronella. Wellington boots worn after dusk afford a good protection to legs and ankles.

Air-currents have a marked effect on sandflies, and Whittingham has shown that the most effective way of ridding quarters of these pests is to create a strong current by means of electric fans.

CHAPTER IX

RAT-BITE FEVER

Synonyms.—Sodoku ; Sokosha (Japanese) ; Cat-bite Disease.

Definition.—An acute febrile disease caused by *Spirillum minus* (*morsus-muris*), inoculated into man by the bite of an infected rat, causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapse and, in some cases, a cutaneous eruption.

History.—This disease has long been known to Japanese physicians. Since its recognition, cases have been reported from India and other countries. In 1915 Futaki, Takaki, Taniguchi, and Osumi demonstrated spirilla in the lymphatic glands from the tenth to the thirteenth day of the illness ; later they found similar, though shorter and stouter, organisms in the blood-stream ; the latter are now recognized as being the young forms of the parasite. This work has since been confirmed by Kaneko and Okuda in 1917, and by R. Row in Bombay. As a result of recent investigations, A. Robertson has shown the organism to be a spirillum, and its correct nomenclature to be *Spirillum minus* Carter, 1887.

Geographical distribution.—Rat-bite fever appears to have a widespread distribution, but it is especially common in Japan. Cases have been reported in Great Britain by Horder, Low, and Atkinson, and from the United States, Germany, Italy, Australia, and East Africa.

Etiology.—*S. minus*¹ is a short, squat spirillum differing greatly from spirochætes, at any rate when in the human body. It measures 1·5–6 μ in length ; the pointed extremities are continued into one or more flagella ; including this, the total length may be 15 μ . (Fig. 48.) The curves are regular, and generally number three or four, or even six or more. It is difficult to demonstrate in the blood in the living state even by means of the ultramicroscope, but it may be seen in the exudate in the neighbourhood of the bite, and in the juice from the superficial lymphatic glands.

Movements.—In the living state the organism, under the microscope, moves rapidly like a vibrio, by means of lashing movements of the flagella ; the body itself is held rigid, and in this manner the movements can be readily distinguished from the vibratile

¹ Formerly known as *Spirochæta morsus-muris*,

motions of the true spirochætes. This fact, together with a certain amount of doubt regarding its method of multiplication, has led to some controversy as to its systematic position. The presence of the spirillum can be easily verified in suspicious cases by inoculation of white mice with any of the material in which it can be seen. Next to mice, white rats and guinea-pigs and monkeys (*Macacus rhesus*) are most susceptible. Usually the experimental animals survive. The organisms appear in the blood-stream about seven days after inoculation, and persist for several months. The disease can be transmitted by the brown rat (*Rattus norvegicus*) and the black rat (*R. rattus* and *R. alexandrinus*), and by the bite of a ferret or of a cat.

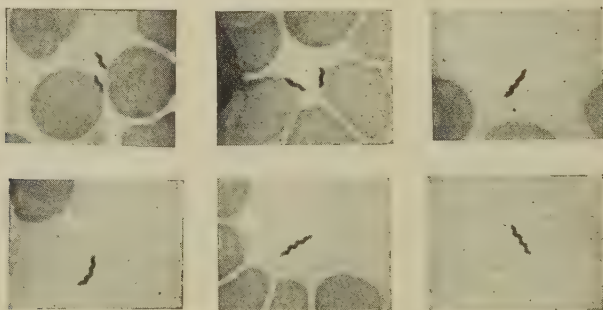


Fig. 48.—*Spirillum minus* of rat-bite fever in mouse. $\times 1,500$.
(Microphoto: Dr. A. C. Coles.)

The organism resembles and is probably identical with *S. laverani* and *S. muris*, which have been found in the blood of rats and mice in various parts of the world.

Joekes has succeeded in cultivating *S. muris* which he found in 25 per cent. of the wild rats in London, by using an inspissated horse-serum slope, as employed for the diphtheria bacillus, over which is poured Vervoort's medium (1-per-cent. peptone to which are added 3 c.c. of normal phosphoric acid). Primary culture is obtained by inoculating the medium with blood from an infected guinea-pig and incubating at 37° C. Subcultures are easily maintained in 1-per-cent. glucose broth.

The immunity conferred on man and on animals during an attack of this fever is permanent, and protects, apparently, against all other organisms of the same type that have been procured from various sources.

Symptoms.—The incubation period varies from one to sixty days; the average being from five to ten days, during which time the wound heals. The cicatrix itself, and sometimes the surrounding

tissues, become inflamed, with formation of blebs and even necrosis. The lymphatics draining the area are implicated, and the glands themselves become swollen and tender. The onset of the fever is characterized by rigors and malaise; the temperature gradually rises in three days to a maximum of 103.4° F., and after a further period of three days ends in crisis with profuse sweating.

After the primary attack a quiescent interval of five to ten days ensues, with subsidence of the local disturbance. One or more relapses (Chart 13), associated with the same symptoms, and in addition a characteristic purple papular exanthem or urticaria on the chest and arms, have been noted.

In most cases the reflexes are increased; there may be pains in the muscles and joints, and hyperæsthesia and œdema of various parts of the body. The death-rate is about 10 per cent. The end is ushered in by delirium, often lapsing into coma.

As in relapsing fever, the organism can be demonstrated in the blood only during the fever, disappearing during the apyretic intervals. The serum agglutinates the spirillum in low dilutions. There is an eosinophilia during the paroxysm and a moderate leucocytosis of about 15,000. It is

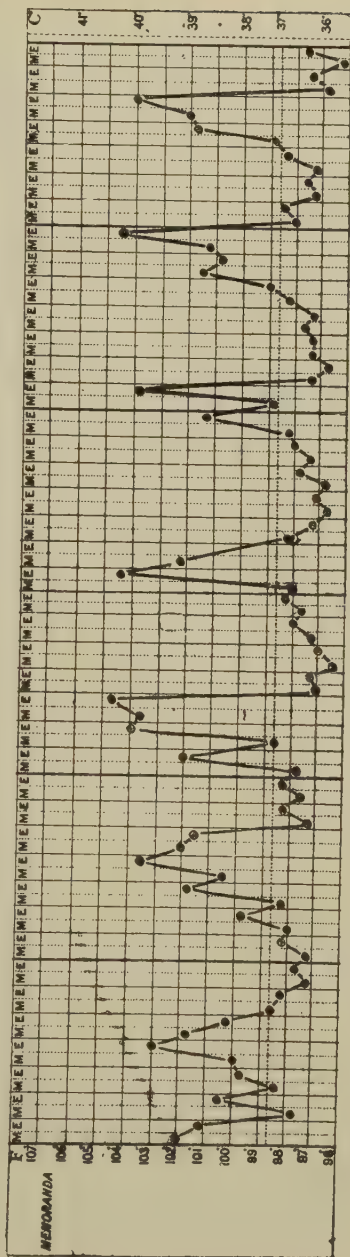


Chart 13.—Rat-bite fever, showing periodic relapses. (By permission of London School of Hyg. and Trop. Med.)

said that the serum in this disease gives a weak positive Wassermann reaction.

Pathology.—In the fatal cases the lymph-glands are swollen, the spleen is enlarged, the liver hyperæmic, and the lungs may show hæmorrhages. The cornea is often involved. The spirilla have been demonstrated in the liver, spleen, kidneys, suprarenal glands, eyes, and testicles.

Differential diagnosis.—This has manifestly to be made from the different forms of relapsing fever and trench fever, with which the temperature chart has much in common. In tropical countries the possibility of a coexistent malarial infection has to be taken into account. The puffiness of the face accompanying the urticarial eruption may simulate Bright's disease.

The reaction occurring around the site of the scar is apt to be confused with erysipelas.

Treatment.—Salvarsan and its derivatives act as a specific. As a rule, one injection of novarsenobillon (0·4 to 0·6 gm.) is sufficient to effect a cure. Occasionally the intravenous injection has to be repeated as a prophylactic measure. A rat-bite should always be cauterized.

CHAPTER X

TYPHUS AND ALLIED FEVERS

TYPHUS has been recognized since the middle of the last century as a disease having distinctive features. Formerly it was confused with typhoid.

Typhus fever has an almost cosmopolitan distribution, but during the last twenty-five years two curiously localized types of disease resembling it have been recognized: one, known as Spotted Fever of the Rocky Mountains, is conveyed by a tick; the second, known as Japanese River Fever, by a small mite. It is proposed to deal with these three forms in one chapter.

I. TYPHUS FEVER

Synonyms.—Typhus Exanthematicus; Tabardillo (Mexico); Brill's Disease.

Definition.—An acute fever of abrupt onset, lasting about fourteen days, and, if not fatal, terminating about the fourteenth day by crisis. The pyrexia is of a remittent type. On or about the fifth day there appears a roseolar eruption tending to become petechial, and spreading from the abdomen over the trunk and extremities. The virus is conveyed by lice.

Geographical distribution.—Typhus has been eradicated in peace times from most civilized European countries, but reappears in epidemic form in periods of stress and famine, as in the Great War. In certain subtropical countries, as in North Africa, it is widespread among the poorer natives. In the equatorial regions it is rare, but in India it occurs in certain districts, and a particularly virulent form is met with in Mexico, where it is known as "tabardillo." Megaw (1921) has described a typhus-like fever occurring in Kumaon and neighbouring foothills of the north-west Himalayas, which he believes to be transmitted by a tick, and recently a similar illness has appeared in Malaya and in Kenya.

Etiology.—Typhus is conveyed by lice (*Pediculus humanus*, var. *corporis* and *capitis*); the virus is filterable, and is infective for monkeys and guinea-pigs; it is present in the blood-plasma, especially in the blood-platelets, during the first five days of the

disease (Bacot and Ségat). A developmental cycle probably takes place in the body-cavity of the louse, which is infective only from the fourth to the seventh day after a meal of typhus blood. Infection is conveyed through the fæces of the louse and is inoculated by scratching. Recent work by Arkwright, Wolbach, Todd, and others points to a minute organism, the *Rickettsia prowazeki*, which occurs in the body of the louse, as the causal organism.

Wolbach and Schlesinger have found that the virus of typhus survives in tissue-plasma cultures for a length of time corresponding to the life of the endothelial cells multiplying in the cultures, and the micro-organism can be found in the endothelial cells in large numbers; coccoid, bacillary, and filamentous forms being noted. Brain-tissue cultures from typhus guinea-pigs have proved most successful. Guinea-pig's blood is used as the source of the plasma, and collected in paraffin-lined tubes, centrifuged, and chilled. The tissue for cultivation is obtained with aseptic precautions and kept immersed in Ringer's solution, the pieces of tissue for cultures being cut into blocks 0.5–1.0 c.mm. in size, transferred to a sterile cover-slip, and covered with sterile plasma. On transferring tissue cultures to fresh plasma, pieces of tissue are first washed in Ringer's solution, and the virus can be kept alive from four to six weeks.

Pathology.—The blood is dark-coloured, and does not clot; the liver and kidneys show cloudy swelling. There is generally a moderate enlargement of the spleen, with hyperplasia of the lymph-follicles; the substance is soft and diffuent. Bronchial catarrh is generally present, with hypostatic congestion of the lungs. There are no changes in the Peyer's patches; the mesenteric glands are not affected, typhus being thus differentiated from typhoid fever. The eruption is due to a localized necrosis of the walls of the smaller blood-vessels, with local collections of lymphocytes and plasma-cells in the adventitia. These nodules, which are characteristic, are found in the brain and viscera, as well as in the skin. The essential lesions are due to a phagocytosis by the vascular endothelium, followed by necrosis of these cells.

Symptoms.—The *incubation period* varies between four and fourteen days, twelve being the average. The period of *onset* lasts about two days, during which time the patient may experience headache, nausea, giddiness, etc. Occasionally, in fulminating cases general convulsions occur, passing into delirium. On the third day the temperature rises suddenly to 103° or 104° F., the face becoming congested, the eyes suffused. (Chart 14.) There is a peculiar stuporose, drunken look, such as is not found in any other disease—except, possibly, plague. The mouth becomes foul, the tongue coated with dense brown fur, the breath offensive. Epistaxis is frequent in some epidemics, and vomiting may be a distressing

feature. For the next twelve or fourteen days the temperature remains raised, with slight morning remissions, and the urine shows a faint cloud of albumin. As a rule the urea and chlorides are increased in amount.

The rash appears on the fifth day, first upon the abdomen and inner aspect of the arms, spreading over the chest, back and trunk, rarely involving the face; it is generally pleomorphic. The term "mulberry rash" has been used to describe the features of the exanthem, but it really consists of roseolar macules, together with a fine irregular dusky mottling underlying the epidermis and generally termed "subcuticular mottling"; it may become

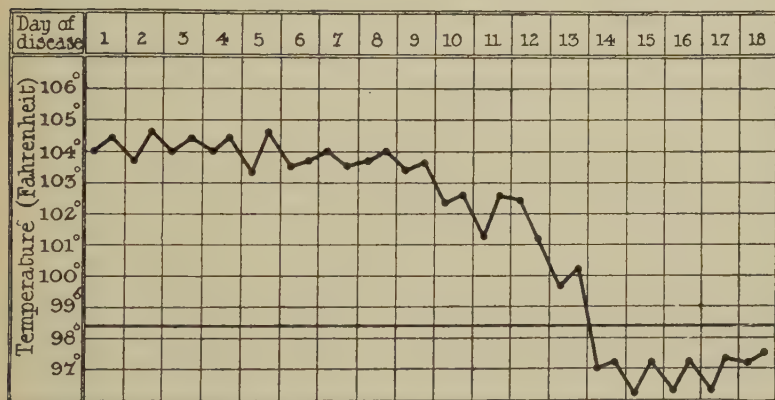


Chart 14.—Typhus fever. (Orig.)

petechial, and involve palms of hands and soles of feet. Exceptionally the rash, instead of being a mixture of purple and copper, is bright red; it may be hæmorrhagic. It fades slowly and may persist for ten days. After the appearance of the rash, prostration and cardiac weakness become pronounced.

In brown- or dark-skinned natives a typhus rash may be very difficult to discern; to make the subcuticular mottling visible, thorough cleansing of the skin and a good strong light are often necessary. Congestion of the arm by means of a tourniquet may render the petechial spots more distinct, a method which has been practised with success in the early diagnosis of the rash in Europeans. In natives the rash is often most pronounced round the umbilical region.

When a typhus epidemic attacks an isolated population, as for instance in a desert oasis, terrible complications due to sepsis and

neglect may ensue; in such circumstances a terminal bronchopneumonia is very common. In the survivors from an attack there may be extreme emaciation, as well as implication of the nervous system—ataxia, violent tremors, mania or dementia. Abortion in pregnant women is common. The young and the aged readily succumb. Parotitis and noma are frequent complications. Relapsing fever and typhus may often coexist. Constipation rather than diarrhoea is the rule, and the mouth becomes very foul, the lips and teeth being covered with sordes. Bedsores are a frequent complication.

On the appearance of the rash there may be signs of bronchitis, and, the mental lethargy becoming more pronounced, the patient sinks into the “typhus” state. Cerebration is slow; hands and tongue are tremulous; the patient is difficult to nurse, and emits an odour which has been compared to “gun-washings,” or that emanating from a cupboard containing well-blackened boots. The odour may not always be distinguishable. In the second week a low muttering delirium supervenes, and the secretion of urine may be diminished or even suppressed. The spleen may be enlarged. Often symptoms of cortical irritation, such as muscular twitchings and incontinence of urine, may be observed.

As the fourteenth day approaches, signs of improvement may set in and the temperature suddenly fall by crisis, or more generally in tropical cases by a rapid lysis. If a fatal issue is to ensue it generally occurs about the twelfth or fourteenth day, or later, when the temperature is subnormal, from exhaustion or cardiac failure. The blood picture shows nothing definite, though there is said to be a moderate leucocytosis of 12,000 to 15,000.

During convalescence the greatest care should be taken against exciting the heart.

Mild cases of typhus, known in America as Brill's disease, in which the rash rarely becomes purpuric, often occur sporadically, and, in fact, are almost constantly to be met with in the endemic areas in the subtropics.

In Algeria a particularly mild form of typhus has been described as “fièvre buttoneuse,” while Fletcher has met with a similar condition in Malaya. He distinguishes between the form of “tropical typhus” encountered in the cities and that met with in the country population. The serum of the former gives the true Weil-Felix reaction, while the latter does not.

Diagnosis.—Typhus in early stages is apt to be confused with measles, enteric, relapsing, or cerebro-spinal fever, or with subtertian malaria. In an epidemic there is rarely any doubt. The more

gradual onset of the fever and the less marked stupor, together with a negative hæmoculture, differentiate enteric. The other conditions mentioned which may simulate typhus may be readily differentiated by laboratory diagnosis. It is said that plague presents the same picture of alcoholic-like intoxication as does typhus, but in the former there is no rash. Influenza of acute onset, such as the epidemic of 1918, may simulate typhus in its early stages. The rashes of Japanese river fever and of the spotted fever of the Rocky Mountains have many features in common with typhus, but difficulty in diagnosis is liable to arise only in the restricted areas in which those fevers occur.

The *Weil-Felix reaction*, first discovered by Wilson of Belfast, is a very real aid to the diagnosis of typhus. A bacillus, *Proteus vulgaris*, now termed X 19, and originally isolated from the urine, where undoubtedly it occurs only as a contamination, possesses in emulsion the extraordinary property of being agglutinated by typhus serum as early as the fifth day of the disease. The test may be performed in test-tubes by the progressive dilution method (p. 868), or with Garrow's agglutinometer. By the latter method an agglutination of 1:20 may be regarded as diagnostic. The maximum agglutination results are obtained from the eighth to the twenty-first day; a titre of 1:2,500 has been recorded; the reaction may be obtainable for sixty days. Occasionally typhus serum may agglutinate cultures of *B. typhosus*.

The appearance, in the blood of typhus cases, of agglutinins specific for X 19 is not accompanied by the formation of specific immune bodies, as has been shown by Fairley, though the latter are produced when a normal person is injected with cultures of X 19. Using an emulsion of this organism as an antigen, a positive complement-deviation reaction may be obtained with the serum of such a person.

There is little evidence, either from systematic blood- and urine-cultures during life, or from the organs post mortem, that this bacillus (*P. vulgaris*), which can be cultivated in artificial media with ease, is the etiological factor in typhus.

Treatment.—As there is no specific drug in typhus, special care must be devoted to nursing. Strict attention must be paid to the hygiene of the mouth. The recumbent position is absolutely essential. Bedsores should be guarded against. It is equally essential that the patient have as much fresh air as is possible. Stimulants must be given to maintain the cardiac action, the favourite being port wine; but care must be exercised that it is not given, as is so often the case, in excess—8 oz. in the twenty-four hours is sufficient. Digitalis or digitalin ($\frac{1}{100}$ gr.) is indicated as a cardiac stimulant. Lumbar puncture may be employed to relieve the delirium and other cerebral symptoms; as a rule there is excess of pressure in the cerebro-spinal fluid. There are no special precautions with regard to diet, which should be nutritious and easily digestible.

Serum treatment has been introduced in epidemics in southern Russia by Asheshov. The serum itself is obtained from patients during convalescence after the temperature has been normal for a period of four to eleven days. When injected in doses of 20–50 c.c. it is said to mitigate the severity of the symptoms, though it does not shorten the course of the disease. This method is applicable to a limited number of cases during an epidemic.

Mühlens reports that two intravenous injections of *novasurol* (1 c.c. of a 10-per-cent. solution) appear to cut the fever short.

Prophylaxis.—This consists almost exclusively in the destruction of body-lice. The body should be shaved—including the pubes and axillæ—and the hair of the head cropped. After a cresol bath the underclothing should be smeared with a preparation consisting of unwhipped naphthaline 4 parts, soft soap 1 part; but whenever possible all clothing, including blankets and bedclothing, should be disinfected, preferably by dry heat. To kill lice and their eggs with certainty, a temperature of 55° C. for 30 minutes, or of 60° C. for 15 minutes, is required. Disinfestation of clothes on a large scale may be accomplished on the railway in luggage vans, by closing the doors and turning on superheated steam from the engine. The use under field conditions of the Serbian barrel, in which the clothes are saturated with steam under pressure from water within the barrel itself, is a practical method. In default of steam, ironing of the seams of the clothing has been found useful. Soaking in 2-per-cent. lysol destroys both the pediculi and their eggs.

A method of prophylactic inoculation against typhus, originally suggested by Hamdi, a Turkish physician, has been practised in southern Russia by Mitchell, Asheshov, and Richardson, and is worthy of further trial. The “vaccine” employed consists of “inactivated” typhus blood. The blood from a patient in the acute stage of the disease is defibrinated, inactivated for half-an-hour at 58° C., and injected in doses of 1, 2, and 5 c.c. at intervals of from four to five days; and it is claimed that a substantial protection against typhus is obtained by these means.

Indian tick typhus (Megaw) closely resembles typhus in its clinical manifestation; it occurs in certain localities year by year and attacks persons who come in contact with the life of the jungle and open country. There is no evidence that it can be communicated from person to person directly. It is not associated with lice, but follows a few days after the bite of a tick. The Weil-Felix reaction is negative.

II. ROCKY MOUNTAIN SPOTTED FEVER

Synonyms.—Rocky Mountain Fever; Black Fever; Blue Disease.

Definition.—A specific fever supervening on the bite of a tick—*Dermacentor venustus*, Banks—and resembling symptomatically typhus exanthematicus.

History.—For upwards of thirty years a peculiar disease, variously named “spotted fever,” “blue disease,” “black fever,” has been recognized as endemic in limited districts of Montana, Idaho, and Wyoming, America. Wolbach described in 1919 a Rickettsia body as the germ-cause of the disease. In 1906 King ascertained that the disease supervened on the bite of *Dermacentor venustus* (*D. andersoni*).¹ (Figs. 309, 310, p. 800.)

Geographical distribution.—The disease has been reported from several of the western states of the American Union—Idaho, Montana, Wyoming, Utah, Nevada, Oregon, Colorado, and Washington States. It is believed to occur also in the Alaska Territory, and in 1916 was definitely proved by Kelly and Cumming to exist in California. It is found principally in valleys and near the foothills of mountains in sharply defined and limited areas. It attacks any age, either sex, and is not directly contagious.

Etiology.—The evidence is now conclusive that the germ of Rocky Mountain fever is introduced by the bite of *D. venustus*. It is only the adult that attacks man (*see* p. 799). The Rocky Mountain goat, the domestic sheep, black bear, coyote, badger, and lynx also serve as hosts to the adult ticks, but the larval and nymph stages develop principally on the ground-squirrel, *Citellus columbianus*, and the woodchuck, *Marmota flaviventris*. The disease occurs in the spring months (March to July), at a time when *D. venustus* is prevalent.

The Columbian ground-squirrel lives amongst birch woods where it digs its burrows. It hibernates in winter and apparently in this state it harbours the virus of Rocky Mountain fever. The woodchuck is really a marmot and is about 2 feet in length. It hibernates in deep burrows over 50 feet in length during the winter.

Wolbach noted small bodies staining with Giemsa in the endothelial cells of the blood-vessels and in the testes of man and of virus-infected guinea-pigs, as well as a general distribution of the Rickettsia organisms in the bodies, salivary glands, and eggs of infected ticks (*Dermacentor*). Two morphological types are recognized: one a lanceolate diplococcal organism found in the circulating blood as well as in the endothelial cells, and containing chromatin-staining substance; the other staining blue, and rod-shaped. Wolbach has named the parasite *Dermacentroxenus*

¹ The names *D. venustus* and *D. andersoni* refer to the same species. The differences in the nomenclature of the tick used by various authors have resulted in a good deal of confusion. *D. reticulatus* and *D. occidentalis*, apparently distinct species, have at various times been incriminated as carriers of the infection.

rickettsi. (Fig. 49.) In conjunction with Schlesinger, he has cultivated the organism in the tissue-plasma of guinea-pig testis, when numbers of filamentous forms of the organism apparently develop in the endothelial cells of the vessel-walls.

Noguchi has cultivated from the intestinal tract of *D. venustus* a bacillus, *B. rickettsiformis*, which resembles the pathogenic *rickettsia*.

According to Ricketts, the virus is easily inoculated into man, and can be passed through an indefinite series of monkeys and guinea-pigs, giving rise in them to the characteristic symptoms, in which a scrotal swelling is held to be pathognomonic. Immunity is conferred upon these animals. The larva, nymph, and adult male and female tick are all of them efficient intermediaries for the parasite. Ricketts suggests—seeing that in one place (Montana) the case-mortality in man is as high as 90 per cent., whereas in another place (Idaho) it is only 5 per cent.—that there are two different species of tick capable of carrying the infection; in the former instance it is *D. venustus*, in the latter *D. maturatedus*. The proportion of ticks infected under natural conditions is small—only 1 in 296 in Ricketts's experience.

In conformity with the seasonal prevalence of the tick, the disease in man is most frequent in April, May, and June.¹

Pathology.—Post mortem, in addition to the skin lesions, there are marked hypostatic congestion of the lungs, subserous petechiæ, softened myocardium, enlarged firm spleen and lymphatic glands, fatty degeneration of the hepatic cells, and congestion

¹ **Tick paralysis.**—According to Hadwen, the tick *D. venustus* as it occurs in the dry district of British Columbia, Keremeos, gives rise to a peculiar form of paraplegia in sheep, which, directly or indirectly, may prove fatal. In the same district it affects man and other animals in a similar way. Todd has called attention to this disease, of which he has collected a considerable number of cases, some of them fatal, caused by the bites of this species as well as of *Hæmaphysalis cinnabarina*. Nuttall, working at Cambridge, England, has confirmed Hadwen's experiments. He placed one of the ticks received from Hadwen on a healthy dog. Twelve days afterwards the dog became completely paralysed in fore and hind legs; it gradually recovered. According to these authors, a similar disease is produced in South Africa by the bite of *Ixodes pilosus*.

This form of tick disease is manifestly different from Rocky Mountain fever, as it is nonfebrile, is unattended with eruption, and is not communicable by inoculation. Possibly it is produced by a poison instilled by the tick during haustellation. The wound it makes is very painful, is attended with œdema and, on forcible removal of the tick, with free bleeding as if some anti-coagulin had been introduced. The symptoms of the disease suggest infantile paralysis.

In sheep, the favourite points of attachment of the tick are on the back along the course of the spine; in man, the nape of the neck.

A somewhat similar form of paralysis is described by Eaton and Dodd as following on tick-bite in Queensland, the incriminated ticks being *Ixodes ricinus* and *I. holocyclus*. Bancroft reports from the same country a similarly-caused form of epileptiform convulsions in cats and dogs.

of the cortex of the kidneys. Constant lesions, both in man and in animals, are hæmorrhages into the genitalia; gangrene of the prepuce and scrotum are often noted. Proliferation of the endothelium of the arteries and veins of the skin and subcutaneous tissues, with accumulation of Rickettsia bodies, is a feature, the cells taking on phagocytic properties and ultimately becoming necrotic. There is a perivascular mononuclear infiltration as in typhus.

Symptoms.—A short period of malaise is followed by chills, which are repeated with diminishing severity at irregular intervals throughout the attack. By the second day the temperature has risen to 103° or 104° F., and by the fifth day to 105° or 107°. A typhoid-like condition, with low muttering delirium and semi-

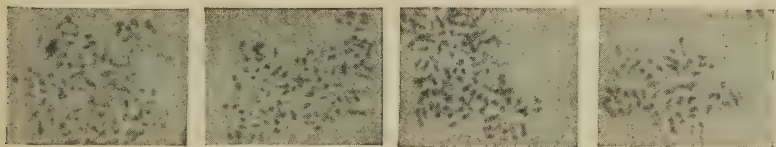


Fig. 49.—Microphoto of *Dermacentroxenus rickettsi*. $\times 2,000$.
(Dr. A. C. Coles.)

consciousness, is rapidly developed. If the patient is to recover, the temperature begins to fall about the end of the second week; fever subsiding usually by lysis.

About the fourth to seventh day an eruption appears on the wrists, ankles, or back, extending rapidly to the trunk, scalp, hands, and feet. At first it consists of minute rose-coloured spots; these soon assume a petechial character and, spreading, tend to become confluent, especially on the more dependent parts of the body and limbs. In other instances the spots remain discrete, and are brownish or purplish in colour, giving to the surface of the body a speckled appearance. A certain amount of icteric tinting of skin and scleræ is also present. During the third week desquamation sets in, the eruption fading as fever subsides. In some cases the skin of the elbows, fingers, toes, lobes of the ears, etc., becomes gangrenous.

Constipation is usual. The liver is slightly enlarged, the spleen markedly enlarged and tender. The scanty, high-coloured urine may contain albumin and casts. Early in all severe cases there is œdema of the face and limbs. Nausea and vomiting set in about the beginning of the second week, and persist in fatal cases. Respiration is rapid. Slight catarrh of the respiratory tract is

present throughout; the pulse loses in volume as it increases in frequency. There is but little diminution in the blood-count, and only a feeble leucocytosis—12,000 to 13,000; the hæmoglobin is slightly diminished.

Complications such as gangrene of the tonsils, scrotum, and prepuce are more common in the milder type of the disease, as seen in Idaho. One attack of the disease confers immunity, and no instance is known of a second attack of this fever in man.

Differential diagnosis.—The sudden onset, the joint pains, and the negative Widal reaction differentiate this fever from enteric; the geographical distribution is the most important factor in differentiating it from typhus. A negative Weil-Felix reaction (agglutination with X19) serves further to distinguish it from the latter disease (Kelly).

Treatment and prophylaxis.—In the absence of a specific remedy, treatment must be conducted on general principles, regard being had to the natural history and character of the disease. Intravenous injections of *mercurochrome 220 soluble* (see p. 257) have been tried in 1-per-cent. solution. Attempts at prophylaxis are now being carried out, based on the above-described mode of transmission. War is being waged on the ground-squirrel and the woodchuck; domestic stock and goats are being systematically dipped to prevent the spread of and, if possible, to exterminate the tick. It should be borne in mind that *D. venustus* does not infest human dwellings.

Frick, finding that *D. venustus*, when placed on the fleece of an unshorn sheep, either dies or remains unimpregnated, and is manifestly on an uncongenial host, suggested, in addition to the measures just mentioned, turning the badly-infected districts into sheep-runs.

Those who work in endemic areas should provide themselves with a working costume consisting of one piece; the trousers should be tucked up inside woollen socks, and the sleeves at the wrists secured with a strap. Tick-bites should be cauterized or excised.

III. JAPANESE RIVER FEVER

Synonyms.—Tsutsugamushi; Shimamushi; Kedani Mite Disease; Exanthematous Glandular Fever.

Definition.—An acute endemic disease running a definite course, and attended with a considerable case-mortality varying from 10 to 52 per cent. It is characterized by the presence on the skin of an initial eschar, supervening on the bite of a species of

Trombicula. This is followed by an ulcer, lymphangitis, fever, a peculiar eruption, bronchitis, and conjunctivitis.

History.—This disease was first described by Palm in 1878, and subsequently, more fully, by Baelz and Kawakami. Ancient records indicate that it has been known for more than a thousand years.

Hatori has published (1919) a very full account of the epidemiology, while Hayashi has described minute intracellular bodies in the endothelial cells resembling the *Dermacentroxenus* of Wolbach.

Geographical and seasonal distribution.—Formerly it was thought that tsutsugamushi was confined to the banks of two rivers on the west side of the island of Nippon, Japan—the Shinanogawa and one of its tributaries, and the Omonagawa. Every spring these rivers inundate large tracts of country, and later in the year hemp is raised on strips of the inundated district. The crop is reaped in July and August, and it is solely among those engaged in harvesting and handling this that the disease occurs. It is not communicable by the sick to the healthy. It now appears that the disease is widely spread in Formosa, and possibly in Korea, both among the Japanese settlers and the aborigines. In Formosa it occurs in the highlands as well as in the coastal plains. The epidemic commences in April and disappears in November. Tsutsugamushi disease has now been reported on certain estates in Malaya. An analogous fever has been described as “pseudotyphoid” in Sumatra by Schüffner, and is carried by mites, *Trombicula deliensis*. The Mosman fever in Northern Queensland may possibly prove to be of the same nature, as also a similar disease in the Philippines, Malaya, and Indo-China.

Etiology.—The Japanese attribute this disease to the bite of an acarus (locally called *akamushi*—red insect), the larva of *Trombicula akamushi*¹ (formerly incorrectly known as *microtrombidium akamushi*), resembling *Leptus autumnalis* of Europe, and popularly known as the kedani mite or “patau” (Figs. 299, 300, p. 794). Men, women, and children are equally susceptible; from their occupation it is commoner in men. New arrivals in the endemic districts are said to be specially liable. One attack does not confer immunity, although it may render subsequent attacks less severe. As yet the virus of the disease, which doubtless enters in the first instance at the site of the primary eschar, has not been definitely determined.

Blood from infected cases injected into rats, monkeys (especially gibbons), and marmosets conveys the disease to these animals, and the parasite can be demonstrated in their tissues as well as in other animals inoculated with an emulsion of the mites. Intradermal inoculation is more successful than

¹ Also known in Japan as *Trombicula coarctata* (Berlese).

subcutaneous (Nagayo and others). Bodies described as rod-, spheroid-, or ring-shaped have been found in the lymphocytes of lymph-nodes and in the mononuclear endothelial cells of the spleen, as well as in the region of the bite. They are said to occur in the blood-plasma, and in severe cases in the red blood-corpuscles. The organism has been provisionally named *Theileria tsutsugamushi*, but is apparently similar to the bodies described by Wolbach in Rocky Mountain fever. Miyajima states that tsutsugamushi is communicable to the monkey by the bite of the insect and also by inoculation from a human patient.

According to Kawamura and his co-workers, the blood of patients is very infective in the incubation period of the disease. The minimum dose capable of infecting monkeys is 0.001 c.c. The infective agent is easily destroyed by heating at 55° C. for ten minutes. The mite occurs numerously on the ears of the field vole, *Microtus montebelloi*, and other rodents—*Mus jerdoni*, *R. rattus rufescens*, *R. decumanus*, *R. agrarius*, which, however, have not been found to be suffering from any particular disease at the time. It also becomes more widely distributed by the agency of a small warbler—*Acrocephalus orientalis*, domestic fowls, a pheasant—*Phasianus formosanus*, and a quail—*Turnix taigoon*. The mite will also attack dogs, cats, and the buffalo. Its life-cycle has now been worked out by Nagayo, Kawamura, and others, and it is known to be the hexapod larva of *Trombicula akamushi*, a red mite 0.9 mm. in length, living in grass, but which is non-parasitic in its habits. Recent work suggests that the virus of tsutsugamushi also occurs in the body-cavity of the adult mite.

In Sumatra and Malaya the vectors *T. deliensis* and *T. schüffneri* frequent the undergrowth and long grass known as "lalang" in clearings of the virgin jungle: they have been found also to infest the crow-pheasant (*Centropus javanicus*) which inhabits that kind of country.

T. deliensis is pale ochre in colour, *T. akamushi*, bright vermillion.

Pathology.—The lesion at the site of the bite undergoes coagulation necrosis, and affects the epidermis, the corium, and the tissues surrounding the puncture. It is well marked off from surrounding tissues by a boundary line. The spleen is generally enlarged, the capsule tense, and the substance soft and friable; not infrequently areas of necrosis are present. The liver is enlarged, and shows cloudy swelling on section. The lungs are congested and frequently hypostatic pneumonia is present. The bone-marrow shows signs of great activity. There is a generalized enlargement of all the lymphatic glands, but those in the neighbourhood of the lesion are especially affected, and may attain the size of a pigeon's egg. The elements most affected appear to be the lymphocytes. Areas of patchy necrosis are frequently encountered.

Symptoms.—The person attacked by the mite does not usually notice the bite, and later only feels a pricking sensation when he happens to touch the spot. The mite, or mites, can easily be seen by the aid of a strong magnifying glass, with their heads and

bodies buried in the skin, but only when they are carriers of the disease do any definite pathological changes take place round the lesions they inflict. After an incubation period of from four to ten days the disease usually begins with malaise, frontal and temporal headache, anorexia, chills alternating with flushes of heat, and prostration. Presently the patient becomes conscious of pain and tenderness in the lymphatic glands of the groin, armpit, or neck. On inspection of the skin of the corresponding lymphatic area there is discovered—usually about the genitals or armpits—a small (2 to 4 mm.) round, dark, tough, firmly adherent eschar surrounded by a painless livid red areola of superficial congestion. Occasionally two or three such eschars are discovered. Although a line of tenderness may be traced from the sore to the swollen, hard, and sensitive glands, no well-defined cord of lymphangitis can be made out. The superficial lymphatic glands of the rest of the body, especially those on the opposite side corresponding to the glands primarily affected, are also, but more slightly, enlarged.

Fever of a more or less continued type now sets in, the thermometer mounting in the course of five or six days to 104° or 105° F. The conjunctivæ become injected, and the eyes somewhat prominent; at the same time a considerable bronchitis gives rise to harassing cough. The pulse is full and strong, ranging rather low—80 to 100—for the degree of fever present. The spleen is moderately but distinctly enlarged, and there is marked constipation.

About the sixth or seventh day an eruption of large dark-red papules, tending to become confluent on the cheeks, and fading on pressure, appears on the face. It extends to the forearms, legs, and trunk, being less pronounced on the upper arms, thighs, neck, and palate. Simultaneously a minute lichenous eruption breaks out on the forearms and trunk. This lasts usually from four to seven days; if but slightly marked, the eruption may fade in twenty-four hours, becoming pigmented.

During the height of the fever the patient is flushed, and at night, it may be, delirious. He complains incessantly, probably on account of a general hyperæsthesia of skin and muscles. Deafness is also a feature.

As the disease advances, the symptoms become more urgent; the conjunctivitis is intensified, the cough becomes incessant, the tongue dries, the lips crack and bleed, and there may be from time to time profuse perspiration. By the end of the second week—sooner or later according to the severity of the case—the fever begins to remit, the tongue to clean, and, after a few days, tem-

perature falls to normal and the patient speedily convalesces. There is a well-marked leucopenia. The red cells are normal, but there is a decrease in the coagulability of the blood. Bronchitis, diarrhoea, or diuresis may occur during the decline of the fever. The circular, sharp-edged, deep ulcer left after the separation of the primary eschar—usually during the second week—now begins to heal, and the enlargement of the glands gradually to subside. The urine is albuminous and gives the diazo-reaction.

Such is the course of a moderately severe case. In some instances, however, the constitutional disturbance is very slight, although the primary eschar may be well marked and perhaps extensive. On the other hand, the fever may be much more violent, and complications such as parotitis, melæna, coma, mania, cardiac failure, or œdema of the lungs may end in death. Similarly, the duration of the disease varies according to severity from one to four weeks, three weeks being about the average. Relapses do not occur.

Pregnant women contracting tsutsugamushi mostly abort and die.

According to Hatori, reinfection may occur.

The death-rate in Japan is high—from 25–30 per cent., but much lower in Sumatra (0–15 per cent.).

Differential diagnosis.—The limited geographical distribution and seasonal incidence of the disease, together with the initial necrotic ulcer and lymphadenitis, should prevent any error in diagnosis. Plague may possibly be thought of in the first instance, but, even if a primary vesicle or ulcer exists in this disease, the matting together and exquisite tenderness of the lymphatic glands should put one on one's guard. Typhus, measles, and dengue may also be thought of.

Treatment.—The site of the bite should be treated by cauterization or extirpation. Salvarsan has been found to be useless. Hayashi and Mukoyama have employed the serum of cattle and monkeys which have recovered from the disease; in severe cases in which it was injected in the early stages, successful results were claimed. Otherwise treatment is symptomatic only.

Prophylaxis.—In a mite-infected country all parts of the body should be properly protected. For this purpose a mite-proof suit has been devised by Hayashi and Nagayo. All articles of clothing used in infected fields should be sterilized, and the parts of the body exposed to mite-bites bathed with Vlemineck's solution. The most effective measure is the burning down of the bushes and grass in the endemic area before bringing it under cultivation.

CHAPTER XI

OROYA FEVER AND VERRUGA PERUANA

MEDICAL opinion in Peru has always regarded Oroya fever and verruga peruana as clinical manifestations of the same disease. For a time this view appeared to be negatived as the result of the work of the Harvard Commission in 1915, but the important work of Noguchi on the cultivation of the virus of Oroya fever and the subsequent production of verruga-like lesions on inoculation into monkeys has certainly settled the question of the unity of these apparently distinct diseases. Mayer and Kikuth have recently in Germany fully confirmed the work of Noguchi in every respect.

OROYA FEVER STAGE

Synonym.—Carrion's disease.

Definition.—An acute specific fever, endemic in certain valleys of the Andes, and characterized by a rapidly developing anæmia of the pernicious type, irregular pyrexia, and great tenderness over the blood-forming tissues. The organism is *Bartonella bacilliformis*.

History.—The first attempt to settle the etiology of this disease was made by the self-sacrifice of Carrion, a medical student who, in 1885, fatally inoculated himself with the blood from a verruga nodule in Lima. From this experiment the Peruvian physicians concluded that the verruga and Oroya fever were different stages of the same disease.

Geographical distribution.—Between the 9th and the 16th parallels of south latitude, and at an elevation of from 3,000 to 10,000 feet, in certain narrow valleys of the western slopes of the Andes, this peculiar fever is endemic. It is therefore found in Peru, Ecuador, Bolivia, and Chile. Its topical as well as its geographical range is singularly limited; it is confined to certain hot, narrow valleys or ravines, the inhabitants of neighbouring places being exempt.

It is said that the disease may be acquired when merely journeying through the endemic districts, more especially if the traveller passes the night there.

Etiology.—Although out-of-door workers are the most subject, all ages, classes, and both sexes, including infants, are liable to attack. During the fever certain rod-like bodies are to be found in a large proportion of the red

blood-corpuscles (Fig. 50), and in endothelial cells of the lymphatic glands. These were first noted by Barton in 1909, and were considered by him to be protozoal in character; these findings were subsequently confirmed by Strong and other members of the Harvard Commission, and the bodies were termed by them *Bartonella bacilliformis*. They somewhat resemble stages of a piroplasm (*Theileria parva*) during its cycle in the lymphatic glands, and similar bodies are found in the blood of normal mice and certain rodents (*Bartonella muris*), which, as Mayer, Borchardt and Kikuth have shown, exist as a latent infection, but which may produce an acute and fatal anæmia, resembling Oroya fever subsequent to removal of the spleen. Two forms are

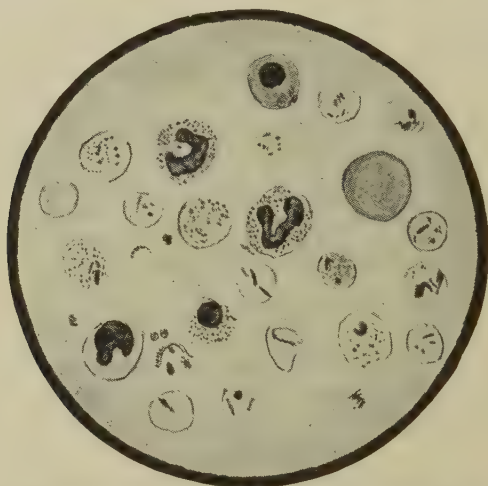


Fig. 50. — Blood-film in Oroya fever, showing bacilliform bodies in red cells. $\times 800$. (Partly after Schilling.)

recognized—one is a rod-shaped, slightly curved bacillary organism $2\ \mu$ long by $0.5\ \mu$ broad, staining with Romanowsky an intense blue, often in branching forms and in chains, but never crossed; the other form is a rounded body about $1\ \mu$ or less in diameter, usually oval or pear-shaped, and containing chromatin granules. Both forms are difficult to distinguish in fresh blood, and show feeble independent movement.

Noguchi regarded *Bartonella* as a bacillus and has recently succeeded in cultivating it on solid media from specimens of citrated blood sent in "cold storage" from Lima to New York. The organism grows best at low temperature on blood-agar media. It is an obligatory aërobe and Gram negative, but stains well with Giemsa. Intravenous injections of cultures into *Rhesus* monkeys, produced irregular fever and extreme anæmia; in the blood-cells the *Bartonella* organisms could be demonstrated. Intradermal injection into the supraorbital tissues gave rise to nodules resembling verruga. (Fig. 51.) In excised nodules *Bartonella* survives for at least fifty-six days at 40°C . Noguchi has further succeeded in conveying the infection to monkeys by the bites of ticks (*Dermacentor andersoni*). Townsend in 1913 conjectured that the insect vector was a sandfly (*Phlebotomus verrucarum*).

The disease is most prevalent from January to April, when the streams are in flood, the air hot, still, and moist, malaria epidemic, and insect life abundant.

Pathology.—A remarkable feature of this disease is the rapidity and extreme degree of blood destruction. In bad cases the blood-count may drop in three or four days to 500,000 per c.mm., the picture being that of a pernicious anæmia. There is a marked polymorphonuclear leucocytosis with disappearance of eosinophils.



Fig. 51.—*Macacus rhesus*, 36 days after inoculation, showing the appearance of verruga peruana on the eyebrow. (Noguchi, *Journ. Exp. Med.*)

In addition to the anæmia, marked changes are present in the liver, spleen, and bone-marrow. In the liver, areas of degeneration and central necrosis are found around the hepatic veins. In the centre of the necrotic areas a yellow pigment resembling hæmosiderin is present in abundance. The spleen is invariably enlarged, and also contains necrotic areas with pigment in the pulp, but the Malpighian bodies themselves are not affected. The lymphatic glands contain large macrophage endothelial cells studded with rod-shaped bodies. The lesions in the viscera are considered by Strong to be due to toxins liberated by the parasite. The bone-marrow shows proliferation, necrosis, and marked phagocytosis of the large endothelial cells.

Symptoms.—The *incubation period* of Oroya fever is about three weeks. Its *onset* is insidious and is marked by malaise, soon followed by a rapidly developing pernicious anæmia and an irregular remittent pyrexia, associated with very severe pains in the head, joints, and long bones. The bone pains are probably con-

nected with the disturbances in the hæmatopoietic system. Very often the initial fever is like that of a malaria infection, and may be the outcome of a double infection in a malarial subject. The most severe types resemble a fulminating typhus and are known as the "severe fever of Carrion." The liver and spleen are enlarged and tender. The anæmia develops with great rapidity. The death-rate varies from 10 to 40 per cent. of those attacked, the end coming within two or three weeks of the onset of the disease. A terminal delirium is often noted. In those cases in which verruga ensues, the fever may last three to four months.

VERRUGA PERUANA STAGE

Definition.—A remarkable granulomatous eruption confined to certain parts of Peru and neighbouring countries. It is associated with hæmorrhages, fever, and joint pains. The disease was known to Pizarro, and is described in Prescott's "Conquest of Peru."

Etiology.—Superficially, the lesions of verruga resemble those of yaws.

Rocha Lima, Mayer, and Werner described chlamydozoa-like cell inclusions in the verruga nodules and considered them to be the cause of the disease. As already related, Noguchi has demonstrated *Bartonella* bodies in experimentally-produced lesions in monkeys. This work has been recently confirmed by Mackehenie, Weiss, Mayer and Kikuth, who have produced nodules in monkeys with human material and demonstrated *Bartonella* bodies within the angioblasts or endothelial cells. Verruga is therefore but a local connective-tissue infection with *Bartonella bacilliformis*.

Strong's experiments upon monkeys showed that by graduated inoculation of verruga material he was able to induce an artificial immunity. Verruga can be conveyed by inoculation to rabbits and dogs, and according to Townsend occurs as a natural infection of native Indian dogs.

Pathology.—Primarily the pathological changes consist in a proliferation of the endothelium of the lymphatic channels, which become obstructed by plasma-cells and fibroblasts, but the structure is much more vascular than that of yaws, which it otherwise resembles. The capillary blood-vessels become dilated, so that the granulomatous tumours are vascular, almost cavernous, and prone to bleed profusely. A feature of the pathological histology is the formation around the blood-vessels of nodules of angioblasts characteristic of the disease. *Bartonella* bodies may be found in the blood-corpuscles after prolonged search (Mayer), but in monkeys, if the spleen be removed, they multiply exceedingly and produce Oroya fever.

Symptoms.—The period of incubation subsequent to Oroya fever is thirty to forty days, but in those cases in which the initial fever is absent it is at least sixty days. The initial stages are characterized by peculiar rheumatic-like pains, together with fever, the pains being apparently the same in character as those of yaws, only more severe. As in yaws, the constitutional symptoms subside on the appearance of the skin lesion. The eruption, like that of yaws (*see* p. 489), may be sparse or abundant, discrete or confluent. As in yaws, individual granulomata may fail to erupt; others may subside rapidly; yet others may continue to increase, and then, after remaining stationary for a time, gradually wither, shrink, and drop off without leaving a scar. If difference there be in their clinical features between verruga and yaws, apparently it is more one of degree than of kind.

The eruption is generally described as being of two types, miliary and nodular—the former not exceeding the size of a small pea; the latter, the rarer form of the two, less numerous, but consisting of much larger nodular masses. The miliary eruption, as a rule, is found most abundantly on the face and extensor aspect of the extremities, less commonly on the trunk.

A pink macule first appears, which later darkens in colour and becomes nodular. These nodules may be flat or somewhat pedunculated. The verruga artificially produced in monkeys by injection of Bartonella bodies is bright cherry-pink in colour.

We find no mention made of the occurrence in yaws of fungating granulomata in any situation but the skin. In verruga it would seem that these vascular lesions may develop on mucous surfaces—in the mouth, œsophagus, stomach, intestine, bladder, uterus, and vagina. (Fig. 52.) Hence the dysphagia—a common symptom—and the occasional occurrence of hæmatemesis, melæna, hæmaturia, and bleeding from the vagina. Relapses both of the fever and of the eruption may occur.

In inoculated monkeys swelling of the lymph-glands is an early and constant symptom.

The tendency to spontaneous hæmorrhage is attributed to the diminished atmospheric pressure at high altitudes, for it is said that when patients descend to the lower valleys or to the sea-level the proneness to bleeding ceases.

The nodular eruption is more chronic than the miliary; individual lesions may grow to the size of a pigeon's egg; they may become strangulated, and a source of danger from hæmorrhage. This type of eruption does not invade the mucous membranes, and is usually confined to the regions of the knees or elbows. It

appears in crops, and the duration of the disease extends over two or three months.

In contrast to Oroya fever, the mortality from verruga is practically nil.

Diagnosis.—The appearances of verruga are so characteristic that it is hardly likely to be mistaken for any other disease. Conceivably it may closely resemble the frambœsiform eruption of secondary yaws; it may also be simulated by multiple warts, molluscum contagiosum, multiple fatty tumours (Dercum's disease), and, according to Strong, it is closely allied to, if not

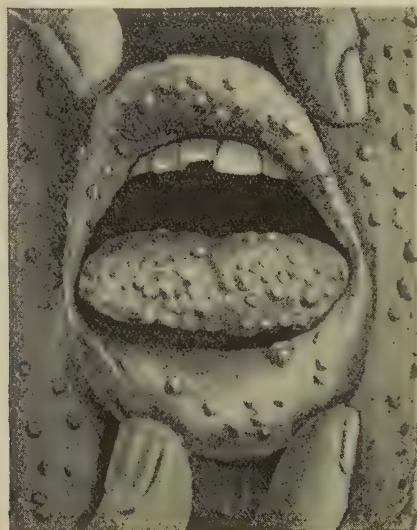


Fig. 52.—Verruga peruana: showing nodules on skin and on mucous membrane of mouth. (After Biffi.)

identical with, Bassewitz's angio-fibroma cutis conscriptum contagiosum. Individual tumours may resemble a fibro-sarcoma or an angioma. The Oroya and verruga stage frequently coexist.

Treatment.—Very little is known about the treatment of these conditions. Small doses of salvarsan, 0.2 grm. intravenously, have been tried with benefit, in the Oroya fever as well as in the verruga stage. When individual tumours begin to ulcerate or become gangrenous they should be excised. Dangerous bleeding may occur, and styptics or compresses may be required to stay the excessive loss of blood. The general bodily resistance should be built up by good food, iron and arsenic injections and other general measures.

CHAPTER XII

PLAGUE

Definition.—Plague is a specific, inoculable and otherwise communicable epidemic disease common to man and many of the lower animals. It is characterized by fever, adenitis, a rapid course, a very high mortality, and the presence of a specific bacterium, *Bacillus pestis*, in the lymphatic glands, viscera, and blood. In a large proportion of cases buboes form in the groins, armpits, or neck.

History.—The first authentic account of plague in Europe relates to an outbreak in A.D. 542, which, starting from Egypt, spread over the Roman Empire. The disease visited England as a widespread epidemic for the last time in 1664–79, and in 1664–5 upwards of 70,000 out of the 460,000 inhabitants of the London of that day perished. In recent years, and from time to time, cases of plague have occurred in the Port of London in seamen from Eastern countries, and plague-infected rats are by no means uncommon in the docks of the metropolis; but, with the exception of a limited epizootic in rats and rabbits, and several fatal cases in man in 1910 in Suffolk, there is no record of plague in Britain, apart from the cases occasionally seen in the seaports, since the seventeenth century.

Geographical distribution.—Probably plague is always present in some part of India and in Uganda, especially among the rude hill-people. It is known to have been endemic in the south-west of China, in the province of Yunnan, for many years. The present extension of plague probably had its origin in that part of China. It is safe to prophesy that plague will continue epidemic in that country for many years to come. Japan and the Philippines were both infected from China.

Imported from Hong Kong, the disease appeared in 1896 in Bombay, and subsequently as a great epidemic spread to Calcutta and to many other parts of India, where it still prevails. The mortality from the current epidemic is numbered in millions. In 1913 plague spread from Negapatam to Ceylon, and in 1914 broke out in epidemic form for the first time in Colombo, where it still remains confined to one portion of the city.

Soon after its appearance in India, plague became extensively epidemic in Mauritius, and it still prevails there at certain seasons.

Mombasa and British East Africa (including Nairobi), the West African colonies, Madagascar, Delagoa Bay, Cape Town, Port Elizabeth, Durban; also Sydney and Brisbane in Australia, and Alexandria in Egypt, have all been invaded.

Until its appearance in Brazil, the Argentine, and other South American countries, and in San Francisco and Mexico, plague had never invaded the Western hemisphere.

Epidemiology and endemiology.—The most potent circumstances which predispose to the epidemic outbreak of plague are extreme filth and overcrowding. In such circumstances the virus, once introduced, tends to spread. With alteration in the habits or circumstances of the population, the disease, after having become epidemic, may die out spontaneously.

Except in the relatively rare pneumonic form, plague is not nearly so contagious as are scarlet fever, measles, and smallpox.

Possibly plague infection may be conveyed in food or drink, or these may be contaminated by infected rats, though it is unlikely that this method plays any important part in the spread of plague. The plague bacillus may be introduced through trifling wounds of the feet.

Age, sex, and occupation have very little influence in plague. The youngest children are susceptible.

Atmospheric temperatures, if very high or very low, seem to have a repressing effect. On the other hand, plague on more than one occasion has flourished during a Russian winter. On the whole, the evidence points to moderate temperatures—50° to 80° F.—combined with a certain degree of dampness as being the principal atmospheric condition favouring epidemic outbreaks and recurrences.

In large towns and in some districts in which plague recurs for several years in succession there is a seasonal periodicity (which may not be the same in all places) of maximum and minimum prevalence.

The *duration of epidemics of plague* is very variable. In large cities—Bombay, Hong Kong, Canton, for example—when fairly established the disease may not relax its grip for ten or more years. In smaller towns it may disappear in a few months.

The *extension of plague epidemics* is peculiar: the disease follows trade routes, and especially the grain trade. Sometimes it may spread rapidly from point to point; more generally it creeps slowly from one village to another, from one street or one house to another. Sometimes it skips a house, a village, or a district.

These and many other facts in the epidemiology of plague are to be explained by the connexion of the disease with the rat

and its flea, and depend in the main upon the migrations of the former and the breeding seasons of the latter.

ETIOLOGY

The micro-organism.—The specific cause of plague is the bacillus which was discovered by Yersin and Kitasato in 1894. It occurs in great profusion in the characteristic buboes—generally in pure culture, although towards the later stages it is often associated with the streptococci and staphylococci of suppuration. It is present, besides, in great abundance in the spleen, intestines, lungs, kidneys, liver, and other viscera, and also, though in smaller

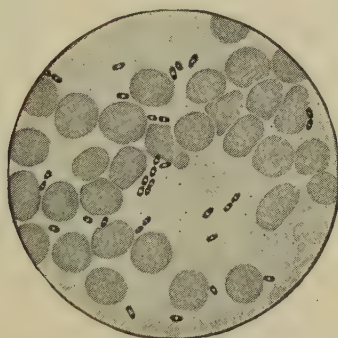


Fig. 53.—*B. pestis* in peripheral blood in septicæmic plague.
× 500. (Microphoto: Dr. J. Bell.)

numbers, in the blood, while in the pneumonic type of the disease it is found in the expectoration in enormous numbers. It may occur also in the urine and fæces; in the latter it may be hard to find by direct observation. Towards the termination of rapidly fatal cases it occurs in great numbers in the blood.

The plague bacillus (Fig. 53), as seen in a blood-film, or in preparations from any of the other tissues, is a short, thick cocco-bacillus (1·5 to 2 by 0·5 to 0·7 μ) with rounded ends, very like the bacillus of chicken cholera. A capsule, or the appearance of a capsule, can generally be made out, especially in bacilli in the blood. The organism is readily stained by aniline dyes, especially by Romanowsky stains, the extremities taking on a deeper colour than the interpolar part, giving it a bipolar appearance. It is usually decolorized by Gram. Epstein regards the bipolarity as a phenomenon not specially confined to *B. pestis*; the fixing and staining of the specimen naturally influence the result.

Culture characters.—When sown on blood-serum and kept at body-temperature, in from twenty-four to forty-eight hours an abundant moist,

yellowish-grey growth is formed without liquefaction of the culture medium. On agar, but better on glycerin-agar, the growths have a greyish-white appearance. In agar-plate cultures they show a bluish translucence, the individual colonies being circular, with slightly irregular contours and a moist surface; on mannite-neutral-red-bile-salt agar the colonies are bright red, but are colourless on a similar medium in which lactose is substituted for mannite. Litmus-milk and glucose-broth are rendered slightly acid, lactose-broth is unchanged. Young colonies are glass-like, but older colonies are thick at the centre and more opaque; they are singularly coherent and may be removed *en bloc* with a platinum needle. Stab-cultures show after one or two days a fine dust-like line of growth. According to Yersin, when sown on gelatin the bacillus gives rise to white transparent colonies which, when examined in reflected light, present iridescent borders. In bouillon the cultures present a characteristic appearance: the liquid remains clear, whilst a granular deposit takes place on the sides and bottom of the tube. Cultivated on broth in which clarified butter or coconut oil is floated, *B. pestis* presents characteristic stalactite growths which gradually fall off, forming a granular deposit. Examined with the microscope, these various cultures show chains of a short bacillus, presenting here and there large bulbous swellings. In gelatin the bacilli sometimes form fine threads, sometimes thick bundles made up of many laterally-agglomerated bacteria, and involution forms are common. The bacillus does not produce spores.

The most favourable temperature for culture is from 36° to 39° C.

The bacillus has a special affinity for rodents, fleas, and man.

Intensification and attenuation of virus.—The virus of plague can be modified by artificial methods: it is well known that a process of this kind takes place in nature, for as a plague epidemic decreases, so the case-mortality falls. It is the early cases that are the most rapidly fatal. Chronic plague occurs in rats in which plague abscesses are found in the spleen and liver without seriously affecting the health of the animal. Although latent, the organism in these cases is potentially virulent for other animals, so that in certain circumstances the virus becomes accelerated. By rapidly passing the virus by inoculation from one guinea-pig to another the rate of its action becomes accelerated, but when grown on plates it has been found by Yersin that rapidly developing colonies of the bacillus possess a diminished virulence, so that eventually they cease to be pathogenic to guinea-pigs. That the gravity of an attack is not affected by the amount of virus introduced was demonstrated by Barber, who succeeded in producing fatal infection in guinea-pigs by the introduction of a single bacillus.

Considerations such as these have led up to the modern prophylactic inoculation against plague.

Norman White believes that there are two biological types of *B. pestis*, the one responsible for bubonic, the other for pneumonic plague.

Experimental plague. Inoculation.—Whyte in 1802 communicated the disease to himself, and died of it. At Cairo, in 1835, two condemned criminals were inoculated from the blood of plague patients; they contracted the disease, but recovered. The deplorable accident in a Vienna laboratory, in October, 1898, by which fatal plague of a pneumonic type was acquired—in what way is not exactly known—from manipulations with plague cultures, goes far to complete the little that was wanting in the chain of evidence that this disease is caused by the introduction of the specific bacillus into the human body.

In the case of the guinea-pig, within a few hours of the introduction of

the virus a considerable amount of œdema is already apparent around the puncture, and the adjacent gland is perceptibly swollen. At the end of twenty-four hours the animal is very ill; its coat is rough and staring, and it refuses food, and presently becomes convulsed. If the body is opened

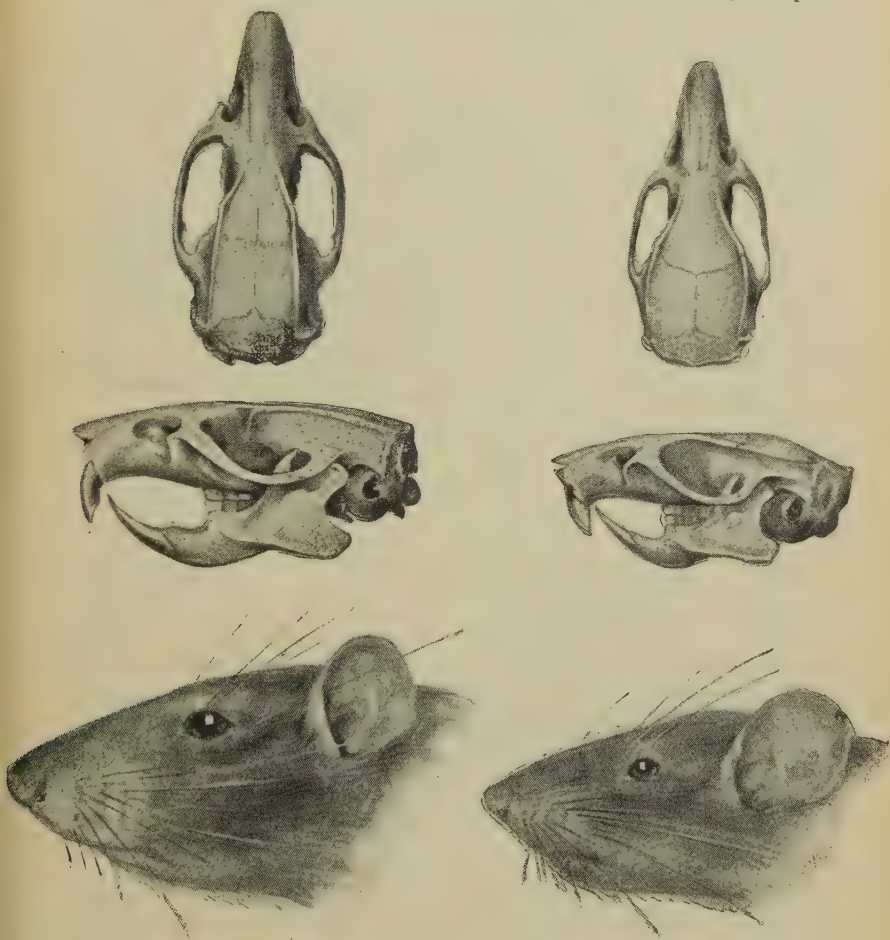


Fig. 54.—*Rattus norvegicus*.

Configuration and anatomical characters of head and skull (nat. size).

Fig. 55.—*Rattus rattus*.

Configuration and anatomical characters of head and skull (nat. size).

immediately after death, a sanguineous œdema is found at the point of inoculation, with hæmorrhagic inflammatory effusions around the nearest lymphatic gland, which is much swollen and full of bacilli. The intestines are hyperæmic; the adrenals, kidneys, and liver are red and swollen. The much-enlarged spleen frequently presents an eruption of small whitish

granulations resembling in appearance miliary tubercles. All the organs, and even any serous fluid that may be present in peritoneum or pleura, will be found to contain plague bacilli. In the blood, besides those free in the liquor sanguinis, bacilli are to be found in the mononuclear, though not, it is said, in the polymorphonuclear leucocytes.

Rôle of the rat in plague.—Although small and circumscribed epidemics of plague may occur without the intervention of the rat, as when it first appeared in Colombo, there can be no doubt that in most epidemics of the bubonic form this rodent plays an important part both in the introduction and in the spread of infection. The species principally concerned are *Rattus norvegicus* (or *decumanus*),

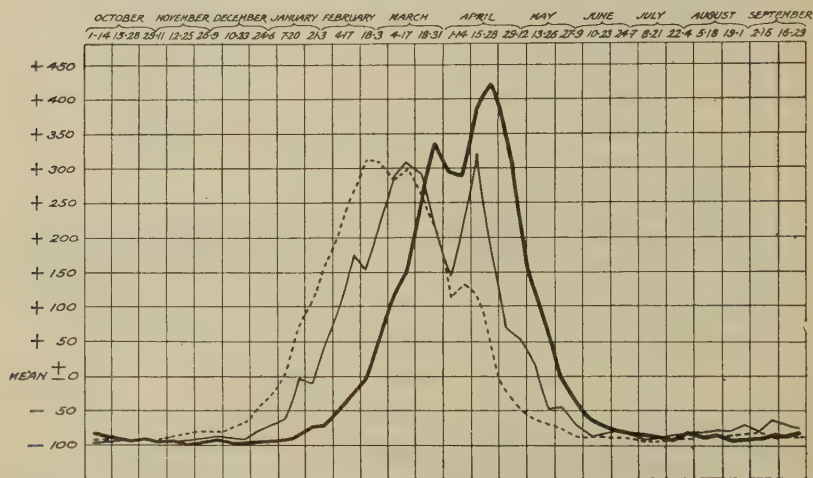


Chart 15, showing progress of plague in rats and man.
 ("Report of Indian Plague Commission.")

..... Infected *R. norvegicus*.
 ——— Infected *R. rattus*.
 ——— Human deaths from plague.

the grey rat, and *Rattus rattus*, the black rat (Figs. 54, 55). The mouse, *M. musculus*, is also susceptible. The bandicoot and muskrat are of little importance in these respects, although susceptible to the infection. In Bombay the epizootic appears first in the *Rattus norvegicus* community, *Rattus rattus*—the more domestic species—being subsequently attacked. Later the disease appears in epidemic form in man. (Chart 15.)

The seasonal prevalence of bubonic plague in rats is marked, and is not due to a periodicity in their reproduction, but is connected with periods in which fleas are most numerous.

In places in which plague epidemics keep recurring year after

year, the local rats acquire a considerable degree of immunity; moreover, this immunity is transmitted hereditarily. Thus, in plague-free towns in India—e.g. Madras and Dacca—the mortality

among the local black rats experimentally infected was 100 per cent., while in plague-stricken towns, such as Cawnpore and Poona, it was much less.

Another observation, already referred to, which together with the foregoing may have important bearings on the spread of plague and the yearly recurrence of epidemics in the same place, is that in certain rats the disease may

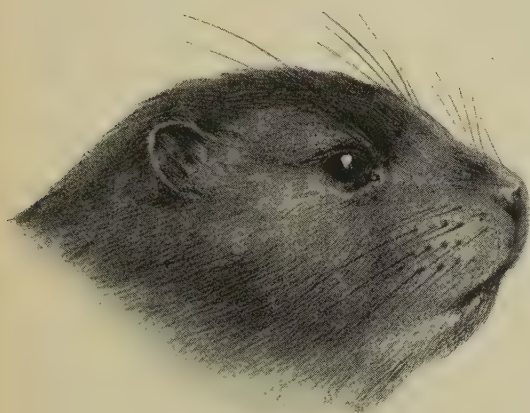


Fig. 56.—*Arctomys bobac*, Siberian marmot (nat. size).

assume a chronic form.

Rats have been known to quit villages in anticipation of the advent of the disease.

Other animals may die of plague during an epidemic; oxen, sheep, deer, pigs, may all be attacked at times. Dogs are immune.

Rôle of the marmot and other rodents.—Mongolian and Siberian pneumonic plague epidemics are associated with the occurrence of the disease in species of marmot called “tarabagan” (*Arctomys bobac*, Fig. 56), and several smaller species (*Citellus citellus* and *C. mugojaricus*) locally known as “susliks,” which can harbour the plague bacillus in their bodies without apparently suffering any ill-effects during hibernation, thus constituting a more or less



Fig. 57.—*Citellus beecheyi*, ground-squirrel of California (nat. size).

permanent reservoir of the plague virus. Possibly the plague infection is transmitted to man by the fleas which infest these animals, but it is more generally considered that the rodent fleas play a minor part and that the infection is transmissible *via* the alimentary tract. It has been shown that in hibernating spermophiles, *B. pestis* loses its virulence and is less easily cultivated. Epizootics of plague in these regions generally begin after hibernation.

The pouched marmot of the Caucasus (*Spermophilus guttatus*) is extremely susceptible to plague infection, and is probably concerned in the spread of the disease in that region. In California the ground-squirrel (*Citellus beecheyi*, Fig. 57), although it does not live near human habitations, infects rats that do, and thereby acts as an important reservoir of *B. pestis*.

In South Africa, especially in the Cape Province, totally different conditions reign, for there it has been found that the rodents of the inland veld have become infected with plague, and by continuously passing the disease from one to another constitute a persistent and dangerous source of human infection. On the high veld the gerbilles [*Taterona lobengulæ* (Fig. 58), and *Desmodillus auricularis*], the ground-squirrel (*Geosciurus capensis*), and the multimammate mouse (*Rattus coucha*) are the most important—the latter forming a link by conveying infected fleas from gerbille burrows into human habitations. In the lower bush country the striped mouse (*Rhabdomys pumilio*) plays the chief rôle, while the springhaas (*Pedetes caffer*), a giant gerboa, on account of its extreme mobility, is capable of widely disseminating plague. Two carnivores, the suricate and the yellow mongoose are susceptible to plague by feeding on dead and dying rodents, and it has been pointed out by Mitchell that the discovery of gerbille remains in the fæces of these animals is a valuable indication of the existence of a rodent epizootic in the veld districts as these animals do not normally eat gerbilles, unless they are sick.

S. African rodents harbour a large number of species of fleas. Of these, three, *Dinopsyllus lypusus*, *Chiatopsylla rossi* and *Xenopsylla eridos* have been found under experimental conditions, capable of conveying plague infection.

The prophylaxis of plague in the wilder regions of the world, to be effective, necessarily entails a knowledge of the habits of these creatures. The ground-squirrels are really spermophiles which constitute a connecting link between the true squirrels and the marmots. Ground-squirrels are generally to be found in prairie-like regions where they form an intricate system of burrows, at the main entrance of which they may be commonly seen standing on guard upright and motionless.

The true marmots such as the "tarabagan" are characterized by the rudimentary character of the thumb, and their small eyes and ears; the tail is bushy and comparatively short. The burrows which they excavate are very deep and are crowned by mounds of earth thrown up by successive generations of marmots and are known as "bootans" in Mongolia. The gerbilles are small jerboas; they are rather smaller than the domestic black rat; the hind legs are long, the front very short. In colour they are pale fawn with white bellies. Their habitat is sandy country where they live in families. Their warrens extend over an area of 30 square yards and to a depth of 3-4 feet. Gerbilles may commonly be seen sitting warily in an upright position with front paws extended horizontally at the mouth of



Fig. 58.—Gerbilles (*Taterona lobengulæ*). Quarter nat. size. (From Publication of South African Institute for Medical Research.)

their burrows. The warrens often harbour ground-squirrels, suricates and mongoose, all four species, apparently, living on friendly terms.

Gerbilles when sick often exhibit cannibalistic tendencies. The multimammate mouse is naturally the wild mouse of the veld and has much the same habits, and in country districts invades human habitations. The striped mouse is diurnal in habit and is more numerous in bushy country, where it usually builds big nests of sticks on the surface of the ground and lives in large families.

In Dakar a shrew (*Crocidura stamplii*) plays a part in the dissemination of the disease.

On observations such as these the modern quarantine against plague has been framed.

Rôle of the flea in plague.—It is now known that plague is not communicable from animal to animal by simple

contact, but is readily communicated by fleas, and principally by *Xenopsylla cheopis* (Fig. 371, p. 840), the rat-flea of the tropics; *Ceratophyllus fasciatus*, the rat-flea of temperate climates; and *Ctenocephalus canis* and *C. felis*, which bite men, dogs, and rats indifferently; these act as passive intermediaries and carriers of the bacillus. *B. pestis* multiplies in the stomach of the flea, retaining its virulence for over twenty days, and is then passed out in the fæces; so that the flea serves not only as a carrier, but also as a multiplier of the germs.

It is difficult to state to whom the credit for the discovery of the transmission of plague by fleas should be given. Yersin and several other observers had found in 1894 that the dejecta of flies fed on infected organs contained plague bacilli. Ogata in 1897 performed experiments with crushed fleas from rats dead of plague. A year later Simond also succeeded in infecting a mouse by injecting an extract of crushed fleas taken from a plague rat, and Gauthier and Raybaud in 1902-1903 conveyed plague from rat to rat by the agency of fleas. Verjbitski in 1914 proved that fleas communicated plague by their bites, while it fell to the Second Indian Plague Commission to establish the rôle of the rat-flea in the transmission of plague to man.

It is stated that the handling of a rat newly dead of plague is fraught with danger, whereas a rat that has been dead for some time and is cold and stiff may be touched with impunity; and it is surmised that the fleas of the newly dead rat are still in its fur, and quit it for the body of the manipulator, carrying on their probosces the bacilli of the disease, which they introduce when they proceed to feed on their new host. When a rat has been dead for some time and the body is cold, the fleas have already forsaken it—hence the impunity with which the rat itself may be handled; but the danger of infection remains in the locality in which it died and where the hungry infected fleas are awaiting an opportunity for a meal. The fact that in man the glands of the legs are usually the first to become implicated in the majority of cases of plague suggests that the virus is generally introduced through the skin of the feet or legs, which are just those parts most likely to be attacked by a flea picked up in walking across the floor of a room in which plague-stricken rats or other animals have died.

Plague epizootics occur in mice, but are not associated with plague in man. *Ctenopsylla musculi*, the mouse-flea, does not readily feed on man. The human flea, *Pulex irritans*, may transmit *B. pestis* under experimental conditions, yet it plays little or no part in the natural spread of the disease.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer fleas from a plague animal on to a healthy animal, or to place the latter in a room in which plague rats have died recently and been subsequently removed. The fleas that have left the body of the

dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected if the precaution is taken to surround the cage with "tangle foot" so as to keep off the fleas; but if it be placed on the unguarded floor, either in its cage or allowed to run about, or even if suspended 2 in. above the floor—a distance not beyond the saltatory powers of the flea—it will become infected.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and œsophagus, these organs becoming blocked with blood-clot containing a pure culture of *B. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection; at the same time bacilli are passed in the fæces and



Fig. 59.—*a*, Flea viewed as a transparent object; the proventriculus and stomach contain a mass of plague-culture. *b*, Flea's stomach, obstructed by growth of plague-culture.

œs., Distended œsophagus containing fresh blood; P.C., obstructing mass of plague-culture.

may infect through any existing abrasion. They further observed that the "blocked" fleas died very rapidly, apparently of thirst, if placed in a warm, dry atmosphere. (Figs. 59, 60.)

In temperate climates fleas are most numerous during the warmer seasons of the year; hence summer and autumn is the bubonic plague season in such climates. In warm climates bubonic plague is most prone to become epidemic at those times of the year when temperature ranges between 10° and 30° C.—temperatures favourable to the multiplication and activity of the flea. Temperatures over 30° C. are unfavourable to the flea, especially if the atmosphere is dry. Pneumonic plague, not being spread by the flea, is not influenced by temperature in this way.

The flea, then, communicates plague either by its fouled mandibles, by regurgitation in the act of sucking, or by provoking scratching and consequent inoculation of the bacilli deposited in its faeces.

It has long been known that large tracts of country and important cities in India, such as Madras, have remained immune from plague, though in constant communication with plague-infected centres. In 1914 Rothschild and Jordan pointed out that the rat-fleas of Indian cities belonged to three closely allied species—*X. cheopis*, *braziliensis*, and *astia*—and soon afterwards Hirst and Cragg pointed out that in those districts in which plague was uncommon *X. astia* replaced *cheopis* as the common ectoparasite of the



Fig. 60.—Edge of mass of plague-culture from flea's stomach. $\times 1,000$.

Figs. 48 and 49 illustrate the method of transmission of *B. pestis* by *Ceratophyllus fasciatus*.

(By permission of Dr. C. J. Martin, "Journ. of Hyg.," 3rd Plague Suppl., Jan., 1914.)

rat. From this and other experimental evidence it is now assumed that this species is unable to convey the plague infection in the same manner as *X. cheopis* (see p. 843).

Bionomics of the rat-flea.—In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months, should the temperature of the air be low at the time. In tropical temperatures the insect can harbour the plague bacillus without feeding on blood for forty-five days.

Apart from the very serious danger arising from vermin affected with chronic plague, which may hang about a house for a long time, it would appear that the house itself does not retain the infection

for any length of time. The Plague Commission has shown that floors of cow-dung contaminated with *Bacillus pestis* do not remain infective for more than forty-eight hours, and that floors of "chunam" cease to be infective in twenty-four hours.

Pathology.—After death from plague the surface of the body very frequently presents numerous ecchymotic spots or patches. The number and extent of these vary, apparently, in different epidemics. In some epidemics the cutaneous hæmorrhages have been both extensive and numerous; hence the name "black death" formerly applied to this disease. The characteristic buboes are generally apparent; occasionally there are also furuncles, pustules, and abscesses. Rigor mortis is usually moderate; sometimes post-mortem muscular contractions, like those in cholera, take place. Post-mortem rise of temperature is often observed. Decomposition is said to set in early.

The characteristic appearance of plague in a necropsy is that of engorgement and hæmorrhage, nearly every organ of the body participating more or less. There is also parenchymatous degeneration in most of the organs. The brain, spinal cord, and their meninges are markedly congested, and there may be an increase of subarachnoid and ventricular fluid. There are numerous and pronounced puncta cruenta on the brain sections; occasionally there may be considerable extravasations of blood into the substance of the brain (mesencephalon and medulla oblongata).

Ecchymoses are common in all serous surfaces; the contents of the different serous cavities may be sanguineous. Extensive hæmorrhages are occasionally found in the peritoneum, mediastinum, trachea, bowel, stomach, pelvis of kidney, ureter, bladder, or in the pleural cavities. The lung frequently shows evidences of bronchitis and hypostatic pneumonia; sometimes hæmorrhagic infarcts and abscesses are found. The right side of the heart and the great veins are usually distended with feebly coagulated or fluid blood. In pneumonic plague the superficial lymphatic glands are not enlarged; the pleural cavities contain blood-stained serum; the infected lungs are deeply congested and oedematous, and at a later stage pneumonic consolidation is found. The bronchi contain blood-stained serum, and the bronchial glands are swollen and hæmorrhagic.

The liver is congested and swollen and its cells are degenerated. The spleen is enlarged to two or three times its normal size. The kidneys are in a similar condition. The mucosa of the alimentary canal as a whole is congested, showing here and there punctate ecchymotic effusions and, occasionally, hæmorrhagic erosions, and even—especially about the ileo-cæcal valve—ulcerations.

Evidence is invariably discoverable of serious implication of the lymphatic system; around the glands there is much exudation and hæmorrhagic effusion, with hyperplasia of the gland-cells, and an enormous multiplication of bacteria.

Symptoms. *Incubation period.*—Symptoms of plague begin to show themselves after an incubation period of from two to eight, rarely fifteen, days.

The average case of plague: prodromal stage.—In a certain but small proportion of cases there is a prodromal stage characterized by physical and mental depression, anorexia, aching of the

limbs, feelings of chilliness, giddiness, palpitations, and sometimes dull pains in the groin at the seat of the future bubo.

Stage of invasion.—Usually, the disease sets in somewhat suddenly with fever, extreme lassitude, frontal or, more rarely, occipital headache, aching of the limbs, vertigo, drowsiness or perhaps wakefulness, or troubled dreams. Rigor is rarely a marked feature; more often the disease is heralded by feelings of chilliness. The face quickly acquires a peculiar expression, the features being drawn and haggard, the eyes bloodshot, sunken and staring, the pupils probably dilated; sometimes the face wears an expression of fear or horror. The patient, if he can walk, drags himself about in a dreamy sort of way, or he staggers like a drunken man. There may be nausea and vomiting; in some instances there is diarrhœa.

Stage of fever.—The stage of invasion may last for a day or two without a serious rise of temperature occurring. Usually it is of much shorter duration; or it may be altogether wanting, the disease developing abruptly without definite rigor or other warning, the thermometer rising rapidly to 103° or 104° (Chart 16), or even to 107° F., with a corresponding acceleration of pulse and respiration. The skin is now dry and burning, the face is bloated, the eyes are still more injected, sunken and fixed, the hearing is dulled. The tongue is swollen and covered with a creamy fur, which rapidly dries and becomes brown or almost black; sordes form on the teeth and about the lips and nostrils. Thirst is intense, prostration extreme, the patient from utter weakness being hardly able to make himself heard. Sometimes he becomes delirious; the delirium may be wildly furious, or fatuous, or of a low muttering type. Coma, convulsions—sometimes of a tetanic character—retention of urine, subsultus tendinum, and other nervous phenomena may occur. Vomiting is in certain cases very frequent; some patients are constipated, others have diarrhœa. The spleen and liver are usually both enlarged. Urine is scanty, but rarely contains more than a trace of albumin. The pulse, at first full and bounding, in the majority of cases rapidly loses tone, becoming small, frequent, fluttering, dicrotic, intermittent. In the later stages the heart may be dilated, the first sound being feeble or absent.

Bubonic plague.—In about three-fourths of the cases, some time between the first few hours and the fifth day, generally within twenty-four hours, the characteristic bubo or buboes develop. Usually (in 70 per cent.) the bubo forms in the groin, most frequently on the right side, affecting one or more of the femoral glands; less frequently (20 per cent.) it is in the axillary glands; and still

more rarely (10 per cent.), and most commonly in children, it is the glands at the angle of the lower jaw that are affected. The buboes are usually single; in about one-eighth of the cases, however, they form simultaneously on both sides of the body. Very rarely are buboes formed in the popliteal or in the epitrochlear elbow glands, or in those at the root of the neck. Occasionally buboes occur simultaneously in different parts of the body.

The buboes vary considerably in size. In some instances they are not so large as a walnut; in others they attain the size of a goose's egg. Pain is often very severe; on the other hand, it is sometimes hardly complained of. Besides the enlargement of the

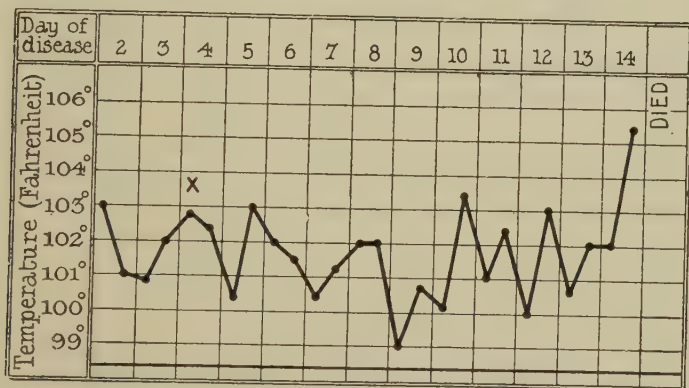


Chart 16.—Septicæmic plague. (Bellingham-Smith.)

x *B. pestis* isolated from the blood.

gland, there is in most instances distinct infiltration of the surrounding connective tissue.

In a very small proportion of cases what are usually described as carbuncles, which are in reality small patches of moist gangrenous skin that may gradually involve a large area, develop on different parts of the integument. These occur either in the early stage or late in the disease. Sometimes they slough and lead to extensive gangrene.

Kirk and Crawford have described a generalized eruption which takes the form of a papular rash on the hands, feet and pectoral region. Should life be continued sufficiently long, the vesicles become converted into pustules. These observations confirm in a remarkable manner, as MacArthur has pointed out, those of the old writers in describing manifestations known in the Plague of London of 1665, as "blains."

In favourable cases, sooner or later, after or without the appear-

ance of the bubo, the constitutional symptoms abate with the setting in of profuse perspiration. The tongue now begins to moisten, the pulse-rate and temperature to fall, and the mild delirium, if it has been present, to abate. The bubo, however, continues to enlarge and to soften. After a few days, if not incised, it bursts and discharges pus and sloughs—sometimes very ill-smelling. In rare instances suppuration is delayed for weeks; whilst in some the bubo subsides after a few weeks, or perhaps months, without having broken down. Convalescence, when it occurs, sets in some time between the sixth and tenth day, although it may be delayed for a fortnight or three weeks. Occasionally a pyæmic condition, with boils, abscesses, cellulitis, parotitis, or secondary adenitis, succeeds the primary fever. The sores left by the buboes and abscesses of plague are extremely indolent and may take months to heal. Secondary pneumonic plague may supervene from which the patient may recover.

Hæmorrhages of different kinds are not an unusual feature of plague—ecchymotic effusions of a purplish or dull-red tint, and varying in size from a hemp-seed to spots half-an-inch in diameter. These hæmorrhages are found frequently in certain malignant epidemics of plague.

Abortion almost invariably occurs in pregnant women; the foetus sometimes shows signs of the disease.

Death may take place at any time in the course of plague. Usually it occurs between the third and fifth day, with symptoms of profound adynamia, heart-failure, or perhaps from convulsions, from coma, from internal hæmorrhage, or, later, from exhaustion consequent upon prolonged fever or suppuration, or from secondary hæmorrhages.

Certain epidemics are distinguished by the large proportion of mild cases, which have been called *pestis minor*.

Septicæmic plague, or pestis siderans.—In this type there is no special enlargement of the lymphatic glands apparent during life, although after death the glands throughout the body are found to be somewhat enlarged and congested. The high degree of virulence and the rapid course of the disease depend on the entry of large numbers of the bacilli into the blood, where they can be readily found during life. The patient is prostrated from the outset; he is pale and apathetic; there is generally little febrile reaction (100° F). Great weakness, delirium, picking of the bed-clothes, stupor, and coma end in death on the first, second, or third day, or, it may be, later (Chart 16). Frequently in these cases there are hæmorrhages.

Pneumonic plague occurs frequently among the marmot-trappers of Northern China, who live under very insanitary conditions. It is especially dangerous to the patients, attendants, and visitors, as well as deadly; dangerous because of the multitude of bacilli which are scattered about in the patient's expectoration, and because the clinical symptoms are unlike those of typical plague and are apt to be mistaken for some ordinary form of lung disease. The illness commences with rigor, malaise, intense headache, vomiting, general pains, fever, and intense prostration. Cough and dyspnœa set in, accompanied by a profuse, watery, blood-tinged sputum. The sputum is not viscid and rusty, as in ordinary pneumonia. Moist râles are audible at the bases of the lungs, the breathing becomes hurried, other symptoms rapidly become worse, delirium sets in, and the patient usually dies on the fourth or fifth day. This is the most fatal as well as the most directly infectious form of plague. Epidemics of 50,000 and more cases have occurred in Manchuria, where the plague bacillus exists as an intestinal infection in the marmot, which acts as a reservoir of the virus. Pneumonic plague has been recorded from Nigeria and the Gold Coast. It has been found that in these countries hæmorrhage into the intestinal canal occurs in about 8 per cent. of plague-infected rats, and in this manner the plague bacillus can be disseminated in dust and inspired by man directly into the lungs. (Connal and Paisley.)

Relapses of all forms of plague, though rare, do occur, and are dangerous.

Mortality.—The case-mortality of bubonic plague varies in different epidemics. It is usually greatest at the beginning and height of the epidemic. The death-rate may be anything from 60 to 95 per cent. of those attacked. Much appears to depend on the social condition of the patient and the attention and nursing available. Thus in a Hong Kong epidemic, while the case-mortality among the indifferently fed, overcrowded, unwashed, and almost unnursed Chinese amounted to 93·4 per cent., it was only 77 per cent. among the Indians, 60 per cent. among the Japanese, and 18·2 per cent. among the Europeans—a gradation in general correspondence with the social and hygienic conditions of these different nationalities. In the South American epidemics and in the recent circumscribed epidemics in Europe the mortality was only about one-third of that obtaining in India and China. Pneumonic plague is generally fatal in from three to four days.

Diagnosis.—The occurrence of fever and adenitis during a plague epidemic must invariably be viewed with suspicion, and

particularly if the fever rapidly assumes an adynamic character. In the early stages diagnosis may be very doubtful, especially in pneumonic plague, and in the countries of high filarial endemicity and in which filarial adenitis is necessarily a common occurrence. Blood-culture is recommended by Onoto by inoculating blood into broth containing 1 per cent. of sodium citrate. In Western America the differentiation of mild cases of plague from tularæmia is important (p. 266). The discovery of the bacillus in the glands, blood, sputum, or discharges is the only thoroughly reliable test. Should a cocco-bacillus be found with the characteristic bipolar staining, it should be cultivated by Haffkine's method in broth on which clarified butter (ghee) or coconut oil is floated. (See p. 242.) In case of doubt, animal inoculation should be had recourse to; a little of the virus from the patient or a culture is rubbed into a shaven area (1 in. square) on the abdomen of a white rat or a guinea-pig. *B. pestis* inoculated in this way kills the guinea-pig in seven days, the rat sooner.¹

B. pestis and *B. pseudotuberculosis rodentium* (the cause of a distinct disease in rodents) closely resemble each other and are scarcely distinguishable by the usual cultural methods. There is no detectable difference between them; neither coagulates milk, but in agar the former produces a more glistening membranous growth. *B. pseudotuberculosis rodentium*, however, produces a clear, yellowish growth on potato. On Drigalski medium it is said to produce blue colonies, and *B. pestis* reddish ones.

The most satisfactory means of differentiation is animal inoculation. Rabbits, guinea-pigs, and white mice are susceptible to *B. pseudotuberculosis*, but white rats are not. The Indian Plague Commission laid stress on the latter point, as these animals are instantly killed by *B. pestis*.

Pneumonic plague differs from other forms of pneumonia in three main characteristics: (1) The patient is extremely prostrate, although his critical state can hardly be accounted for by such physical signs as are present in the chest; but by the time definite involvement of the lung can be demonstrated, he generally dies.

¹ *Post-mortem indications of plague in the rat.*—Before rats suspected of being plague-infected are handled, they should be immersed in disinfectant to destroy ectoparasites.

The lymphatic glands should be first exposed. If the rat is infected, subcutaneous injection around the glands is generally recognizable. If the gland is itself inflamed, this is almost diagnostic of plague; in which case the liver will be of a yellow colour and sprinkled with innumerable pinky-white granules. The spleen is enlarged, congested, and occasionally granular. Serous or blood-stained serous effusions are present in 72 per cent. of such rats; if, on microscopical examination of scrapings from glands or spleen, bipolar-staining bacilli are detected, the case is probably plague. Too great stress must not be laid on bipolar staining alone, as this feature depends somewhat on the method of staining; it is best demonstrated by the Leishman eosinazur stain.

(2) The sputum is watery, never thick, and soon becomes very blood-stained. (3) Pleural effusion is usually present in plague pneumonia.

Treatment.—The treatment of plague is mainly symptomatic. The asthenic tendencies of the disease must ever be borne in mind, and depressant remedies of all kinds carefully avoided.

During the earlier stages, when headache and perhaps high fever are urgent, much relief may be obtained from ice-bags to the head and neck. If it be deemed advisable to attempt to lower the temperature, sponging of the body every hour with warm water is a much safer measure than the employment of antipyrin and similar drugs. Vomiting is usually relieved by a full dose of calomel followed by a saline. If not, or if diarrhoea be present, Lowson recommends ice pills and an effervescing mixture containing morphia and hydrocyanic acid. Sinapisms to the epigastrium are useful. In collapse, stimulants of various kinds, including strong ammonia to the nostrils, and ether hypodermically, are indicated; they sometimes succeed in resuscitating a sinking patient. Given with judgment, morphia is by far the best hypnotic. Hyoscine ($\frac{1}{200}$ to $\frac{1}{75}$ gr.) or chloral (20 gr.) and bromide of potassium (30 gr.) are of service for the same purpose. Diarrhoea, if urgent, is best treated by intestinal antiseptics, as salol in 10-gr. doses every four hours. The buboes in the early stage may be treated with applications of glycerin and belladonna. Should they become red and inflamed, they must be poulticed and, on softening occurring, incised and dressed with iodoform. Indolent bubonic swellings should be treated with iodine liniment. Feeding and stimulation are to be conducted on ordinary principles. The injection of iodine into the buboes has been advocated. Iodine and a solution of camphor and thymol are mixed in equal parts, then injected directly into the bubo in doses of $\frac{1}{2}$ to 1 c.c., according to the age of the patient. Intravenous injections of iodine have gained a certain reputation. A 1-per-cent. solution with double the amount of potassium iodide is used and injected in doses of 5 to 10 c.c. daily for four days.

Serum-therapy.—Yersin, Calmette, and Borrel immunized a horse by intravenous injections of living virulent cultures and produced an effective antiserum. It must be given intravenously in large doses (100–250 c.c.), and frequently repeated. The injections, in order to be effective, must be made early in the course of the disease.

Mercurochrome 220 soluble (dibromo-oxy-mercury-fluorescein). The success attending the intravenous injection of this drug

in various septicæmic states led to the hope that it would prove of use in septicæmic plague. The drug is given in a 1-per-cent. solution in water and the tolerated dose is 2 to 5 mg. per kilo of body-weight. It has been given to a few cases of plague with encouraging results. The dose is 20 c.c. of a 1-per-cent. solution, an amount which can be increased in subsequent injections.

General prophylaxis.—The prophylaxis of plague, as of other infectious diseases, has to be considered from the standpoint of the community and also from that of the individual. As regards the former, it includes measures for preventing the introduction of the virus, for staying its spread if introduced, and for securing its destruction.

Quarantine.—Modern systems of land or sea quarantine directed against plague take cognizance of the facts that the incubation period of the disease may extend to ten days, and that plague affects certain of the lower animals as well as man. Ten days is the minimum period that should elapse between the time of departure from an infected place, between the date of the last death, or between the arrival of a ship or batch of travellers with cases of plague in progress among them, and the granting of free pratique. Moreover, as Kitasato has shown that the specific bacillus persists in the bodies of those who have recovered from plague for at least three weeks from the cessation of the active disease, convalescents should be isolated for a month before they are allowed to mingle with an uninfected community.

Although Kitasato has stated that the plague bacillus perishes in four days when dried on cover-glasses and protected from sunlight, and in from three to four hours when exposed to sunlight, experience has shown that under certain conditions, as yet unknown, it will survive outside the body for a very much longer period, apparently a year or more. There is a considerable mass of evidence tending to prove that clothes, skins, textile fabrics, and similar materials may preserve the virus in an active state for several months.

In ships coming from an infected port the rats, mice, and similar vermin should be destroyed, thrown overboard and sunk before harbour is entered. The generation of sulphurous-acid gas under pressure, especially by the Clayton system, has been found useful for their destruction.

The most suitable and practicable disinfectants are steam, 1 : 1,000 corrosive sublimate in carbol-sulphuric acid, lysol, chloride of lime in 1-per-cent. solution, carbolic acid 5-per-cent., and formalin 2-per-cent.

On plague breaking out in a small village community, as soon as the disease is recognized, measures should be taken to prevent the inhabitants leaving the locality and thus disseminating it. There is little danger of this until the inhabitants become alarmed by a rapid extension of the disease. If possible, after the patients have been isolated in a special hospital, the village should be evacuated for a month. The safest and most thorough form of disinfection is by fire, and in the case of an isolated village prompt destruction of the infected houses by fire is the surest method of stamping out the infection. The clothes and bedding of all patients should be burned. The dead should, with as little delay as possible, be buried in deep graves or cremated. Isolated observation camps should be organized, in which "suspects" and "contacts" may be segregated for a time equal at least to the incubation period of the disease. War should be waged against all rats and mice, and their corpses burned.

In the event of an outbreak in a town, it must be borne in mind that plague, once established in human beings, is communicable to others and to rats by means of the expectoration, by the discharges from the bowels, by the urine, and by discharges from the buboes or glandular swellings; and that a plague in rats usually precedes plague in human beings. In addition, therefore, to prompt notification of plague patients, a system designed to obtain information as to the occurrence of plague in rats should be instituted. Every rat destroyed must be bacteriologically examined.

For the detection of plague-infected houses, guinea-pigs, which do not harbour fleas as a rule, are turned loose in warehouses as convenient traps for rat-fleas.

In India the compulsory inspection of all dead bodies prior to burial has been found a valuable measure for discovering infected houses and localities.

Destruction of vermin and other measures in anticipation of the introduction of plague virus.—The campaign against rats is usually carried on by the employment of rat-traps and rat-catchers, and the cautious laying down of poisons such as arsenic, phosphorus, and baryta. As no one method is satisfactory, it is usual to employ several at the same time. The pumping of SO_2 gas under pressure is useful for ships and for warehouses. So long as the sulphurous-acid gas is dry and is not used on damp articles, no damage is done to merchandise. Care has to be taken with damp things, as they may get discoloured.

Where possible, houses and warehouses should be made rat-proof

—not an easy measure, considering the burrowing and climbing habits of the rat. *Rattus norvegicus* can penetrate ordinary lime-mortar or soft brick, but is stopped by cement and concrete. Its burrows may attain a depth of 18 in. *Rattus rattus* is not so active in this respect. Simpson recommends that walls should be at least 6 in. thick when made of hard brick or concrete, and that they should extend to not less than 18 in. below the level of the ground floor, and the latter should be paved with concrete 3 in. thick, covered with $\frac{1}{2}$ in. of cement. All ventilators should be protected with iron gratings, and all openings around wires and pipes cemented. The mooring cables of ships should be shielded in such a way as to prevent egress or ingress of rats, and all gangways should be taken up at night or when not in use. Native food-stores are, as a rule, set out on poles and can be protected from rat-invasion by the introduction of suitable wooden discs. The sprinkling of chloride of lime in the vicinity of the burrows has a deterrent effect.

In South Africa rigorous measures have been adopted by the Health Department to prevent the spread of rodent plague; they have endeavoured, apparently with success, to place a barrier in the shape of a gerbille-free belt between the mountain range and the sea. Gangs working under departmental rodent officers employ two main methods—poisoning and gassing. The poison is prepared by spreading strychnine-impregnated grain by dropping it into gerbille burrows. Near homesteads, gassing is performed. A Capex cartridge is lighted, plunged into a burrow and the opening closed with earth.

Attempts have been made to set up in rats an epidemic disease, other than plague, which should not be communicable to man: for this purpose the bacillus discovered by Danysz was recommended by him; but experiments on these lines have not been successful.

Prophylactic measures based on a consideration of the flea fauna.—Should further research demonstrate the inability of *X. astia* to transmit plague, it should be possible to divide a country into potential and non-potential plague zones by a survey of the rat-flea population. The energies of the Sanitary Department can by these means be focussed on the danger spots.

Personal prophylaxis.—As regards the individual, all unnecessary visits either to plague patients or to plague neighbourhoods should be avoided and, if possible, prevented. The attendants on the sick ought to take care that the ventilation of the sick-room is thorough, that cubic space is abundant, and that the utmost cleanliness is practised. Nurses must not hang over patients unnecessarily; they must also be careful to seal up and cover any wounds, no matter how trifling, they may have on their hands. Stools and urine must be disinfected, and hands frequently washed.

To obviate risk from wounds and to prevent the access of fleas and similar suctorial insects, those engaged on plague duties should wear boots and have the legs protected by trousers tied tightly round the ankles or, better, by puttees. Leather gloves are advisable if there is much handling of furniture or of anything likely to abrade the skin. *Cats or dogs should not be allowed near plague patients.* In the interests of public health it is imperative to isolate all cases of bubonic and septicæmic plague and their contacts.

The attendants on pneumonic cases should provide themselves with masks of muslin, three- or four-fold, changed when at all damp, and also with goggles to protect the eyes. In pneumonic plague epidemics general inoculation with plague vaccine is advisable. In Mukden a mask of absorbent cotton-wool (16 by 12 cm.) enclosed in muslin, and retained in position by a many-tailed gauze bandage, together with goggles, rubber gloves, and cotton uniform, proved thoroughly effective. Evacuation of the people from insanitary and overcrowded dwellings and installing them in camps where better hygienic conditions can be arranged is imperative. Churches, schools and theatres must be closed. Cordons within the affected area, to limit the infection to a circumscribed portion, may assist.

Haffkine's inoculations.—Early during the Bombay epidemic Haffkine introduced a system of prophylactic inoculation which is of proved value, both in reducing the number attacked with plague to the extent of from 77 to 85 per cent., and in diminishing by 80 per cent. the mortality in those attacked. It consists essentially in the subcutaneous injection of six-weeks'-old cultures of plague bacilli incubated at 25–30° C. and killed by heat—65° C. for one hour; carbolic acid 0·5-per-cent. is then added; up to 4 c.c. are injected according to the size and age of the individual. The Indian Plague Commission reports strongly in favour of these inoculations, which furnish a protection that lasts about twenty months. Glen Liston stated that in the inoculated the incidence of plague was 8 per 1,000 of the population concerned, whereas it was 34 per 1,000 in the uninoculated in the same communities; the case-mortality in the inoculated was 39·5 per 100 attacked, in the uninoculated 78 per 100. The best results are obtained from a two-months' growth which has been stored about eighteen months. The prophylactic needs great care in its preparation. Its storage in hermetically sealed bottles should be insisted upon, and every bottle ought to be tested before use. The resulting reaction is sometimes severe.

So far, Haffkine's prophylactic is the one most frequently used and gives the best results,

Those in attendance on plague patients should receive 20 c.c.

of Yersin's anti-plague serum, and 3 c.c. of Haffkine's vaccine on the same day; ten days later a second dose of vaccine should be given. Attendants should wear lysol-impregnated gowns fastened at the wrist, ankles and neck; rubber gloves and gum-boots. They should not shave, but they should disinfect themselves and their clothes daily.

DESCRIPTION OF THE COMMONER SPECIES OF RATS CONCERNED IN THE SPREAD OF PLAGUE

An intimate knowledge of the appearance and habits of the many species of rats is hardly necessary to the tropical specialist: considering the important rôle several species play in the spread of plague he should, however, be able to identify the more domestic varieties. For this purpose the following Table, contributed by Mr. M. A. C. Hinton, will be found useful:

Rattus rattus, Linn.—Build slender; muzzle sharp; ears large, translucent; tail usually much longer, never much shorter than head and body; hind foot (heel to tip of longest toe, without claw) 35–40 mm.; weight of adults rarely more than 8 oz. Indigenous, wild, more or less arboreal in Indo-Burmese countries. The chief domestic races are distinguished as follows:—

A. Back reddish or greyish-brown.

a. Under parts pure white or pale lemon. *R. r. frugivorus* Raf. (= *tectorum*). Common in Mediterranean region.

b. Under parts darkened.

a¹. Ventral hairs with rusty tips. *R. r. rufescens* Gray. Common rat of Indian houses.

b¹. Ventral hairs without rusty tips. *R. r. alexandrinus* Geoff.

B. Back black; under parts dusky or slate-grey. *R. r. rattus* Linn. Essentially a domestic form which has been evolved in cold temperate countries.

The forms *frugivorus*, *alexandrinus*, and *rattus* have now acquired an almost world-wide distribution; *frugivorus* is the least, *rattus* the most modified race. These are climbing rats, common on ships; frequent in dwellings in warm countries, and not shunning man; they are of especial importance as plague-carriers; attain sexual maturity early (min. weight sex-mature = 70 gm.); breed throughout the year; gestation about 21 days, but with concurrent lactation about 31 days; litter of from 4 to 11; average litter 5 or 6.

Rattus norvegicus Berkenhout (= *decumanus*).—Robust; muzzle blunt; ears small, opaque; tail noticeably shorter than head and body; hind foot 40 to 45 mm.; weight of adults commonly 17 oz., often much more; colour brown or grey above, silvery below. A melanic form (often confused with *R. rattus*) quite common.

Indigenous to Central Asia; now common in all temperate countries. Infests drains and waterways; common in cellars and basements, but shunning mankind as a rule. Breeding and gestation as in *R. rattus* (min. weight sex-mature = 100 gm.); litter of from 6 to 23; average litter 8 to 10.

RAT DESTRUCTION

Terriers may be used, the rats being driven out of their holes by flooding from a watercart. Cats are useful, but it must be remembered that they too are susceptible to plague. Traps of all descriptions are of value, and rats readily enter a funnel-shaped trap showing a light at the far end. Runs may be made with double closing doors, or gins or nipper traps may be placed in the path of rat-runs. One of the most modern methods is the use of lithographic varnish or "ratsticker." The varnish is spread on a board in a place frequented by rats, with a piece of cheese or other material as a bait. On coming into contact with this substance, the rat becomes hopelessly entangled and its squeals attract other rodents to the rescue, so that they in turn become trapped. Rat traps should not be handled except with gloves. They may be covered with mud or anointed with oil of aniseed which removes the human smell.

Baits.—A good bait is one which differs from food usually found on the premises. In fish shops, meat, cheese or bread should be used. In grain stores, bloaters, cheese etc. Dry bread is always acceptable, while oatmeal, and tallow can also be used. It is said in the tropics that tomato is specially tempting.

Poisons.—*Squill* pancakes are made with beef dripping to which has been added 20 per cent. of finely chopped *Scilla maritima* (red variety). The pancakes are cut into baits each $\frac{1}{2}$ -inch square. Various squill preparations are on the market. Squill is mixed with equal parts of milk, and 8 lb. of bread, soaked, for every gallon of solution. One-tenth of a milligramme of extract of squill will kill a rat.

Barium carbonate, 1-2 gr. kills a rat. Cats and chickens can stand 10-15 gr., whilst dogs can take 100 gr. This poison drives rats to seek water so that they die in the open. A 10-50-per-cent. mixture of barium carbonate with fatty basis (*i.e.* tallow) forms one of the safest and most effective rat poisons. "Zelio" paste or poisoned grain (Bayer) in which the grain is thoroughly soaked is said to be absolutely tasteless and readily eaten by rats. The bait is set at night and removed in the morning. After touching the poisoned bait the hands should be washed.

Effective but dangerous to stock.—(a) Strychnine and barium—Battle's vermin killer. (b) Arsenic and barium—"Rough on Rats." (c) "Extermo," "Rodine," "Farmer's paste," "Roth's paste," and "Sandford's paste."

Partly effective but dangerous to man.—The virus of Danysz and similar viruses, which are bacillary in origin, vary very much in lethal effects and have been known to cause "choleraic" symptoms in man. In the tropics they require frequent subculture.

Various poisons for use in selected cases.—(a) Arsenic, 20 per cent. with meal. (b) Dish of oatmeal mixed with sugar, grated Parmesan cheese, and a small quantity of strychnine. (c) Dish of chicken heads. A pinch of strychnine should be placed in each neck with a drop of blood.

FLEAS

Readers seeking information upon the natural history and classification of these insects are referred to p. 839.

CHAPTER XIII

TULARÆMIA AND MELIOIDOSIS

I. TULARÆMIA (Francis, 1921)

Synonyms.—Deer-fly Fever ; Pahvant Valley Plague.

Definition.—Tularæmia is a specific infectious disease of rodents, caused by *Bacterium tularense*, and is transmitted from these animals to man by the bite of infected blood-sucking insects, or by the handling or dissection of infected jack-rabbits.

History and geographical distribution.—*B. tularense* was discovered by McCoy and Chapin in 1911 in a plague-like disease of rodents, more especially the ground-squirrels, of California. As far as is at present known, the disease is confined to the States of California, Indiana, Kentucky, Ohio, and Utah, in the United States. Recently (1926), it is said to have been found in Japan (Francis and Moore).

Epidemiology and endemiology.—In its endemic areas the disease is most prevalent in the months of June, July, and August, when it is conveyed by a blood-sucking fly, *Chrysops discalis*, from one infected jack-rabbit to another. In this manner the disease is usually transmitted to man. Tularæmia is a disease of the rural population, particularly attacking field workers, but it has also been recorded among dealers in rabbits who handle infected jack-rabbits, and those who prepare their skins for market.

Etiology.—*B. tularense* is a small non-motile, Gram-negative organism, measuring 0.3–0.7 μ in length ; when stained in the tissues it gives the appearance of being surrounded by a capsule. Though normally occurring as a rod-like structure, it frequently assumes a coccus shape. It stains best in tissue preparations with Giemsa's stain, but in smears from cultures it shows up well with aniline gentian-violet.

The organism is difficult to cultivate ; it will not grow on plain agar or in bouillon, and, until recently, had been cultivated only upon the coagulated yolk of hen's eggs, but now Francis has succeeded in getting an abundant growth upon serum-glucose-cystine agar. The cystine medium is inoculated with the heart's-blood of the infected animal, or a small piece of the liver or spleen is rubbed on the surface and allowed to remain in contact with the

medium. Growth appears about the third day, and flourishes luxuriantly on subcultures without the addition of fresh animal tissue. In order to ensure the primary growth, it is necessary that a piece of animal tissue be added to the medium.

Composition of cystine agar.—Cystine agar consists of beef-infusion agar, having a pH of 7·6, to which 0·02 per cent. of cystine is added, after which it is sterilized for fifteen minutes in a steam sterilizer, and subsequently incubated for twenty-four hours to ensure sterility.

Cultures of *B. tularensis* are extraordinarily infectious, and should be handled with great care.

The organism is pathogenic for guinea-pigs, rabbits, white rats, mice, ground-squirrels (*Citellus grammurus beecheyi*), the gopher (*Thomomys bottæ bottæ*), Rhesus monkeys; while Norwegian rats (*R. norvegicus*), calves, pigs, goats, cats, dogs, and pigeons are found to be refractory. The organism is transmitted in a mechanical manner by *Chrysops discalis*, as well as by the stable-fly, *Stomoxys calcitrans*, the bed-bug, *Cimex lectularius*, the squirrel-flea, *Ceratophyllus acutus*, the rabbit-louse, *Hæmodipsus ventricosus*, and the mouse-louse, *Polyplox serratus*.

The nasal secretion and the urine of infected mice and rabbits are infective for other animals.

Pathology.—The pathological appearances of infected guinea-pigs and rabbits at autopsy much resemble those of plague in the same animals. In an experimentally-infected guinea-pig there is hæmorrhagic œdema at the site of inoculation, with blood-stained peritoneal exudate, and diffusely enlarged spleen, in which characteristic small necrotic foci can be found. Similar lesions may be detected in the liver; on microscopic section of these organisms a dense infiltration with polymorphonuclear cells can be found, but the organisms can with difficulty be detected. In the spleen of the mouse, on the other hand, little or no leucocytic response occurs; and when stained with Twort's light-green neutral-red stain, *B. tularensis* can be readily demonstrated in large numbers.

Symptoms.—Unrecognized cases of tularæmia probably are common in the endemic areas, for it may occur as a generalized disease without local lesions, or local lesions may be present with a secondary lymphadenitis, which may not cause grave constitutional disturbances. As a rule, in the cases which have been so far recorded, a definite type of fever is present. The onset is sudden, with headache, backache, and fleeting pains, remarkable lassitude, and pyrexia which may last for three weeks or more; the extreme range of temperature is about 104° F. The pyrexia may subside to normal, or nearly so, from the third to the sixth day. The pains

commence at some particular point, and persist for two weeks to a month, though localized ones of greater or lesser degree may recur for the succeeding twelve months. Epistaxis and dizziness are common; the weakness and lassitude persist for weeks after the pyrexia has subsided, and it may be months before the normal health is restored.

Such is the description of the generalized disease as it is met with in man. When infection results from inoculation, the effect is purely local; an inflamed papule occurs at the site of inoculation, with secondary lymphadenitis. Following the bite of an infected chrysops or other fly on some exposed surface of the body, the onset is sudden, with pains and fever. The patient may be prostrated and have to retire to bed; the lymph-glands draining the bitten area subsequently become inflamed and swollen, and suppuration may occur.

Three cases of laboratory infection have been recorded in England. Though the debilitating effect is very marked, only one death in a series of seven cases reported from Utah has been recorded, and this took place from apical pneumonia. Infections of the eye and conjunctiva, causing acute conjunctivitis, have been recorded by Vail, Lamb, and others.

Diagnosis.—The diagnosis is most readily effected by inoculating material from the patient's ulcer, or gland-juice obtained by aspiration, into guinea-pigs, mice, or rabbits, thereby producing generalized disease in these animals, when the organism may be isolated with ease from their tissues on special media. The organisms are rarely present in the blood of human cases. Agglutination tests can readily be performed: the serum of patients suffering from the disease will agglutinate suspensions of the organism in high dilutions, but, as pointed out by Ledingham, where cultures of *B. tularensis* cannot be obtained, the spleens of infected mice contain the organisms in such large numbers that an emulsion may be made of the spleen itself in formalized citrate solution. On centrifuging the emulsion there may be a dense deposit of organisms, which can be used for the purpose of agglutination.

The diagnosis of this condition has to be made from plague and from rat-bite fever. In both cases alike it depends upon the recognition of the respective specific organisms.

Treatment.—This is symptomatic only. The patient should be kept in bed for several weeks after the subsidence of the fever. Convalescence should be prolonged.

Prophylaxis.—Prevention depends upon the avoidance of contact with infected rabbits in the endemic area. The dangers of

experimental work with *B. tularensis* in the laboratory have already been sufficiently emphasized.

II. MELIOIDOSIS

Synonyms.—Stanton's Disease; Pneumo-enteritis; Pseudo-cholera.

Definition.—This is a rare, glanders-like disease occurring in Burma, the Malay States and possibly Ceylon. The name melioidosis was suggested by Stanton and Fletcher in order to describe its close relationship to glanders (Greek, *malis* or *melis*). According to Alcock the correct but inelegant terminology ought to be "melidoidosis."

History.—This disease is due to *Bacterium whitmori* (Whitmore, 1911), found at autopsies of beggars in Rangoon. In 1917 Stanton and Hennessy found similar organisms in patients dying from choleraic symptoms. According to Krishnaswamy the disease is specially common in Rangoon.

Etiology.—*Bacterium whitmori* closely resembles *B. mallei*. It is a small bacillus about the same size and shape as the latter organism, and occurs in very large numbers in all the acute lesions of the disease. On culture it also resembles the glanders bacillus very closely, but it is more actively motile and liquefies gelatin more rapidly. It grows luxuriantly upon peptone agar, forming a dense wrinkled culture, especially when the medium contains glycerin; on broth cultures a pellicle is formed. Brown, Duncan and Henry have shown that *B. whitmori* can be distinguished from *B. mallei* by means of its behaviour on a peptonized medium containing 1-per-cent. sodium fumarate. This organism is pathogenic for most laboratory animals; for guinea-pigs, at any rate, the infection is more rapidly fatal than is glanders, but in each case, in the male guinea-pig, acute orchitis is produced—the so-called Strauss reaction.

The organism is excreted in the urine and faeces of infected laboratory animals, while several cases of natural infection in these animals, especially rats (*Mus griseiventer* Bonhote), cats and dogs have been observed.

Pathology.—The lesions produced appear to vary very considerably. Apparently, numerous small pulmonary abscesses roughly resembling those of miliary tuberculosis, are produced. The organisms have been recovered from the blood, urine, sputum, and fluid from cutaneous vesicles of patients dying from the disease.

Symptoms.—The accounts so far published of the symptomatology are extremely meagre. The first cases observed by Stanton in 1917 were suffering from an acute diarrhoea, with collapse roughly resembling that of cholera, and it appears that several patients who recovered from the initial intestinal attack died later from a form of septicæmia with pulmonary lesions resembling tuberculosis. During 1921 a few more cases were encountered, with similar symptoms. Only two patients are known to have recovered. Delirium and mania appear to be frequent terminal symptoms. What appears to be a chronic form of the disease is also known; in this the lesions are confined to the skin and subcutaneous tissues, leading to cutaneous abscesses and collections of pus in the liver, lungs, and spleen. The disease is said to be specially common in morphia injectors. How man is infected, as a general rule, is still uncertain.

Diagnosis.—This is obviously best carried out by isolation of the bacillus from the fæces, urine, or blood, and differentiating it from the glanders bacillus. Stanton and Fletcher report that the blood-serum agglutinates cultures of the organism in high dilution (1 : 2,500 to 1 : 3,000), a fact which is extremely useful in diagnosing the disease. Differential diagnosis from malaria, typhoid, dysentery, general tuberculosis, plague, cholera and even liver-abscess, may be necessary.

Treatment.—Recent cases have been treated by Stanton with autogenous vaccines, which are said to modify the acuteness of the disease.

Prognosis.—Most patients die within ten days of the onset; in chronic cases they may be ill for three to eight months or more.

CHAPTER XIV

UNDULANT FEVER

Synonyms.—Febris Undulans; Malta Fever; Mediterranean Fever; "Abortus Fever."

Definition.—A disease of low mortality, indefinite duration, and irregular course, undulant fever is the result of infection by a specific germ—*Brucella melitensis*.¹ In its more typical form it is characterized by a series of febrile attacks, each individual attack, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia, also of uncertain duration. Common and characteristic complications are a rheumatic-like affection of joints, profuse diaphoresis, anæmia, liability to orchitis, and neuralgia. Although only occasionally fatal, the disease is a fruitful source of inefficiency and invaliding.

History and geographical distribution.—Formerly confounded with typhoid and malaria, undulant fever has been established as a separate disease by the labours of various observers—Bruce (1887), Hughes, Gipps, Wright, Semple, and Bassett-Smith. Latterly Evans has emphasized the close relationship of the organism to the *Brucella abortus* of cattle. Undulant fever appears to be more widely distributed than was formerly thought to be the case. Undulant fever is not confined to Malta, or even to the Mediterranean; it occurs in Italy, France, Spain, the Red Sea littoral, India (Punjab), China, South Africa, Somaliland, West Africa, the West Indies, the Philippines, South America, the Brazils, the United States, especially in New Mexico and Texas, and even in England.

Epidemiology and endemiology.—The following figures, supplied by Bassett-Smith, show the importance of undulant fever in former years to our naval and military services in the Mediterranean :—

INCIDENCE OF UNDULANT FEVER

	Army				Navy			Total days sickness
	Strength	Cases	Deaths		Strength	Cases	Deaths	
1900 ..	9,203	171	10	..	14,250	356	6	.. 22,998
1901 ..	9,384	288	10	..	14,070	286	3	.. 16,987
1902 ..	10,889	198	10	..	18,470	436	3	.. 27,432
1903 ..	10,608	507	11	..	18,410	400	6	.. 30,541
1904 ..	10,615	429	15	..	19,590	430	9	.. 28,458

¹ The organism was formerly thought to be a coccus and was known as *Micrococcus melitensis*, but according to Evans and Myer it is a small bacillus.

The most susceptible age is between the sixth and the thirtieth year. Length of residence does not influence susceptibility. In Malta the natives suffer as well as visitors. In Malta and other places where the disease is endemic this fever occasionally assumes an epidemic character. The period of its greatest prevalence in Malta is the season of lowest rainfall, embracing June, July, August and September, the disease differing in this respect from typhoid, which, in that island, is more prevalent during the succeeding months. Undulant fever is not confined absolutely to the summer months; cases occur all the year round. The disease tends to occur in particular towns or villages, in particular houses, barracks, hospitals, and rooms, and in particular ships, manifestly originating in limited foci of infection. Evidence has accumulated to show that milk is the most important medium. Certain ships were notorious foci of the disease. All classes are liable; the officer and his family as well as the soldier in barracks or the sailor on ship-board. The organism has been found in mother's milk, so may presumably be transmitted to sucklings.

Although the possibility must not be ignored, undulant fever is not generally transmitted directly from one person to another; that is to say, is not, as a rule, directly communicable from the sick to the healthy. The germ is readily conveyed by inoculation; the prick of a contaminated needle will suffice. Moreover, it is a well-recognized fact that, of all infections, undulant fever is the most easily acquired in the laboratory from the handling of cultures. Living emulsions of the micro-organism should never be handed round for class work; similarly, infection may be conveyed by sucking a thermometer recently used by a patient. A very striking circumstance is that in some hospitals the nurses and attendants in the fever wards are ten times more liable to contract the disease than people not so employed.

Milk.—It is now known that the infection is most usually conveyed in milk, and it has been suggested that it may be introduced in other kinds of food, or in water. Facts point very distinctly to goat's milk as the most important medium. The organism is present in the milk of 10 per cent. of Maltese goats. Monkeys are easily infected by feeding them on such milk. Immediately on the goat's milk supply to the naval and military hospitals in Malta being stopped, the cases of locally acquired undulant fever practically ceased. Formerly this fever was very common in Gibraltar. The milk supply of the garrison at that time was largely from goats imported from Malta. Gradually these goats have died out or been got rid of, and no more

Maltese goats have been imported. Concurrently with this there has been a marked and proportional reduction of undulant fever cases in the garrison. There is one well-authenticated instance of wholesale infection from this source in the case of the s.s. *Joshua Nicholson*, which shipped 65 goats in Malta; an epidemic of undulant fever broke out on board, and nearly all those who drank the milk of the goats were attacked. The possibility of the disease being acquired from milk derived from cows suffering from *abortus* infection is still undetermined.

Cheese.—There is a considerable amount of evidence that undulant fever can be acquired by eating cheese made from the milk of infected goats. Several varieties of cream cheese made in the South of France, and even ripened cheese such as “Camembert,” have fallen under suspicion.

Manure.—In the department of Aude near the Pyrenees, cutaneous infection by manure soiled by urine of infected goats and sheep is regarded as possible.

Etiology.—Bruce in 1887 demonstrated the presence in the spleen in undulant fever of a special bacterium—now called the *Brucella melitensis*, and by a series of experiments proved that it was the cause of the disease. Unfortunately, as the bacterium occurs only sparsely in the general circulation (unless in the earlier stages, when the temperature is high), to search for it in the blood in the later stages of the disease does not aid in diagnosis. The organism is present in abundance in the spleen pulp, and also in the lymphatic glands, in which it persists longer than elsewhere, and from both of which it can be recovered by cultivation. Bruce found it in the spleen in ten fatal cases. His results have been confirmed by many other observers. Injections of pure cultures give rise to a similar disease in monkeys and other animals, from whose blood the bacterium can be recovered, cultivated afresh, and, on injection into other animals, will again give rise to the disease. In five recorded instances, inoculation—intentional and accidental—of cultures of the bacterium into man has been followed by the characteristic symptoms after an incubation period of from five to fifteen days.

A variety of the organism, *Brucella paramelitensis*, which gives different serological reactions from those of the original strain, has been recognized as responsible for those cases of clinical undulant fever which do not give an agglutination reaction with cultures of *melitensis*.

Br. melitensis measures $0.33\ \mu$ in diameter. (Plate XIV, Fig. 2.) It occurs generally singly, often in pairs, sometimes in fours, but never, unless in culture, in longer chains. It is Gram-negative and readily stained by a watery solution of gentian-violet, and is best cultivated in a $1\frac{1}{2}$ -per-cent. very feebly alkaline peptonized beef agar; in this medium, some time after inoculation, it appears as minute, clear, pearly specks. After thirty-six hours the cultures become a transparent amber; later they are opaque. No liquefaction occurs in gelatin. The individual colonies are small, round, somewhat raised discs growing to 2–3 mm. in diameter about the ninth day. The optimum temperature for growth is 37°C . In bouillon it may produce a general turbidity. As a rule, the organism cannot be cultivated under anaërobic conditions.

At one time believed to be a delicate organism, recent investigations have shown that the bacterium can live for a long time in water, in dust, or on the clothes of patients, and that it is not killed by cold or desiccation. Moreover, it is now known to be excreted in the urine of man in 10 per cent. of convalescent cases, and to occur in great abundance in the milk and urine of apparently healthy Maltese goats (50 per cent.), cows, and in the urine of apparently healthy men. It is also found in dogs (9 per cent.), sheep, and horses. These facts account in part for the great frequency and dissemination of the disease in such insanitary places as Malta, to which place they specially refer.

Br. melitensis can be cultured from the blood-stream during the height of the fever in a considerable proportion of cases; for this purpose 5–10 c.c. of blood should be withdrawn from a vein, and well diluted in flasks, each containing 50 c.c. of bouillon; these should be examined daily during a week's incubation. It has occasionally been obtained from the fæces and the urine; of the latter a catheter specimen should be incubated in broth for a period of several days. The serum of undulant-fever cases, as well as the milk of infected goats, will agglutinate it. The organism has been recovered from the gall-bladder by Eyre. Amongst the smaller laboratory animals, the guinea-pig is highly susceptible to inoculation—a minute dose injected intraperitoneally causes prolonged infection.

Br. melitensis is stated by Evans, Myer, Shaw, and others to be morphologically, culturally, and serologically similar to *Bacillus abortus* (Bang) (now known as *Brucella abortus*), the organism of contagious abortion in cattle. The three strains, *melitensis*, *paramelitensis*, and *abortus*, are separable one from another only by means of absorption tests. Cultures of *Br. abortus* are agglutinated in high dilutions of the serum of patients suffering from undulant fever. (Plate XIV, Fig. 1.)

It is well known that *Br. melitensis* may produce abortion in goats, though the animals themselves may exhibit no other clinical changes of disease; the same is found to be the case with animals infected with *Br. abortus*.

Abortus fever.—During recent years the close connection between contagious abortion disease of cows and pigs, and undulant fever in goats and sheep, has attracted much attention. On epidemiological grounds, Bevan in 1922 suggested that the undulant fever of Rhodesia, which had recently become prevalent, was caused by *Br. abortus*. No goats are kept on the ranches in which human cases of undulant fever were observed, while the organisms obtained from blood-culture were found to be identical with *Br. abortus*. Direct infection of two medical students with *Br. abortus* and the subsequent development of a fever of the undulant type has been observed in America, and finally the Editor has recorded cases of undulant fever in England which could only be attributed to infection from *abortus*-infected cow's milk. In Southern France, where undulant fever has recently become alarmingly prevalent, the spread of infection is attributed to ewes which excrete the



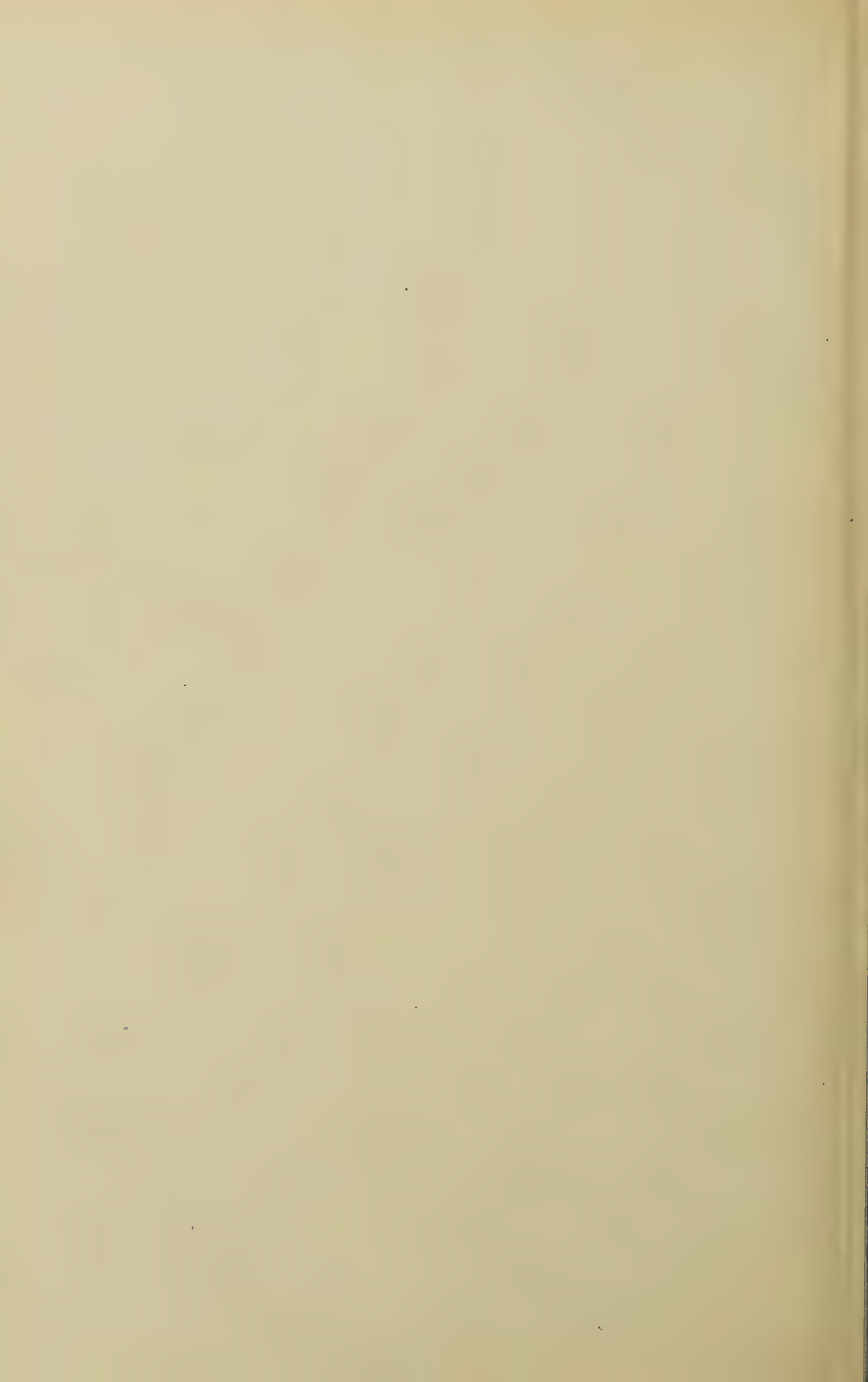
Fig. 1.—*Br. abortus*. Human Rhodesian origin. Twenty-four-hour growth. Shows rods, some 3μ in length. $\times 1,500$.



Fig. 2.—*Br. melitensis*. Human Peruvian origin. Twenty-four-hour growth. Shows coccoid forms. $\times 1,500$.

APPEARANCE OF BRUCELLA ABORTUS AND BR. MELITENSIS ON CULTURE.

(Dr. J. T. Duncan.)



organisms in the urine. Whether they are the *melitensis* or *abortus* type has not yet been determined.

Differentiation of *Brucella abortus* from *Brucella melitensis*.—*Br. abortus* is usually somewhat larger than *Br. melitensis*, being from $0.4\ \mu$ to $0.6\ \mu$ in thickness, and varying in length from $0.8\ \mu$ to 2.5 or even $3\ \mu$. The organism is remarkably pleomorphic; involution forms are of unusual occurrence. (Plate XIV.) The organism is isolated from the milk and uterine discharges of infected animals. Normal strains of *Br. abortus* of bovine origin cannot be grown in primary culture at the ordinary carbon-dioxide tension of the air, and to ensure growth it is necessary to raise the proportion of carbon dioxide to 5 per cent. or 10 per cent. by volume. The carbon-dioxide requirements diminish as the strain is propagated on artificial media. The simplest method of growing this organism is in a Bullock's jar in which culture have been placed for incubation, and adding a sufficient amount of pure carbon dioxide to produce the optimum concentration.

The organism grows best on glucose agar by adding 2-per-cent. glucose to a simple meat-extract agar medium set to reaction of pH 7.4, or on Filde's medium. On potato slopes of alkaline reaction, differences in the growth character of *Br. abortus* and other organisms of the group may be found in week-old cultures; the former gives a uniform creamy-yellow growth, while *Br. melitensis* and *Br. paramelitensis* yield a greyish-chocolate or even black growth.

The formation of hydrogen sulphide from proteins or aminobodies containing sulphur is one of the most important biochemical reactions. The organism is grown on Staffsseth's liver-infusion agar medium at a reaction of pH 6.6 and, after sowing, a strip of lead-acetate paper is introduced into the tube. After forty-eight hours' incubation a distinct blackening of lead acetate occurs in tubes sown with *Br. abortus*.

Diagnosis.—The diagnosis of undulant fever from typhoid is an important practical matter; it is exceedingly difficult in the early stages. Principal reliance has to be placed on the characteristic temperature curve, the presence or absence of rose spots, of diarrhoea, of joint complications, of sweats, the locality where and the season in which the disease was contracted, and, if available, the agglutination test.

An *intra-dermal* or "melitene" reaction has been introduced. For the purpose 0.5 c.c. of a killed broth-culture, containing half-a-million organisms, is injected into the skin. If the reaction is positive, a red oedematous area results at the site, and persists for several days. Adequate controls with broth and cultures of other organisms should be performed in adjacent areas of skin.

Hæmoculture.—During the early stages of the disease the organism may be recovered from the blood-stream. For this purpose 1–5 c.c. of blood should be drawn off by means of an aseptic syringe and with great precaution distributed into several flasks of broth. The broth should be incubated, twenty-four hours, or for as long as five days, and subcultures be made from time to time on trypsin-agar slopes. On the fifth day, on further incubation, minute dewdrop-like colonies should become apparent, and the emulsion

should be tested against a specially prepared immune serum in dilutions from 1:40 to 1:400. It is said that cultures from the blood-clot may sometimes give better results than those from the whole blood. The organism may be obtained by splenic puncture, though this method is rarely justifiable.

Agglutination test.—Agglutination, if performed by the macroscopic method and with modern technique, will generally give positive results, though this reaction is not quite so reliable as the Widal test in typhoid fever. There are several important points which it is necessary to remember in connexion with the reaction.

Strain of organism employed for agglutination.—The serum, as a rule, contains no agglutinins till after the second week of the disease. It may be necessary to employ several strains of *Br. melitensis*, as well as cultures of *Br. paramelitensis*.

As other serums are known to agglutinate the organism in low dilutions, it is recommended that the blood be heated to 56° C. for half-an-hour before being used for the test, in order to destroy non-specific agglutinins. The occurrence of paradoxical reaction (or zone of no reaction) may be a source of error, but only in higher dilutions, and it is possibly due to the presence of anti-agglutinins. It is necessary, therefore, to employ a considerable number of dilutions. The test is most readily performed by Garrow's method.

According to Ledingham the serum of tularæmia agglutinates *Br. melitensis*.

After the fever has gone on for several weeks, diagnosis is, of course, easier; in the early stages, on clinical grounds alone, and apart from the agglutination test, it may be, as already stated, almost impossible. It may be that only on the post-mortem table have we the relative assurance, from the absence of ulceration in the ileum, that we have had to deal with a case of undulant and not typhoid fever. Tuberculosis, abscess, empyema, malaria, relapsing fever, and all the causes of continued high temperature of a septic type, have to be carefully excluded in attempting a diagnosis. The possibility of the concurrence of another infection—typhoid, for example—must not be overlooked.

Pathology.—The disease has almost no pathological anatomy. The spleen is the only viscus which is distinctly diseased. In undulant fever this organ is enlarged (average 17 oz.), soft and diffuent; on microscopical examination the lymphoid cells are found to be increased in number. There may be some congestion and even ulceration of the intestinal mucosa, but this is not an essential feature. Other organs show chiefly cloudy swelling, and glomerular nephritis may be present.

Symptoms.—The period of *incubation* in the naturally-acquired disease is difficult to fix. Cases have occurred as early as six days after arrival, others as late as fourteen and seventeen days after leaving Malta. Some hold that the disease may remain latent for

months. It begins generally with lassitude and malaise, such as we associate with the incubation of many specific fevers, particularly typhoid. There are headache, boneache, anorexia, and so forth. Pain in the eyes, especially on lateral movement, is very characteristic. There may be a peculiar sensitiveness of the alveolar margins of the jaw and painful movement of the temporo-mandibular joint. At first the patient may go about his work as usual. Gradually the daily task becomes increasingly irksome, and he takes to bed. Headache may now become intense, and, in addition, the patient will suffer from thirst and constipation. At the commencement the symptoms, except that there is very rarely diarrhoea, resemble those of typhoid. There are no rose spots, however, then or at any subsequent period. There is evidence, in the coated tongue which looks as if covered with white paint, in the congested pharynx, the anorexia, and the epigastric tenderness, of gastric catarrh; and the occasional cough and harsh, unsatisfactory breathing at the bases of the lungs indicate some degree of bronchitis or of pulmonary congestion. There may also be delirium at night. The fever is usually of a remittent type, the thermometer rising towards evening and falling during the night, and the patient becoming bathed in a profuse perspiration towards morning. The spleen and the liver, but especially the former, are somewhat enlarged and, perhaps, tender. Lumbar pain may be severe, while insomnia is a distressing feature.

After a week or two of this type of fever, specially distinguished by pains and perspirations, the tongue begins to clean and the appetite to revive; but, notwithstanding these signs of amendment, the patient still remains listless and liable to headache and constipation. He continues feverish and at times perspires profusely. Gradually, however, although the patient is anæmic and weak, subjective symptoms become less urgent; he sleeps well now, he has no delirium at night, and he can take food, and this although the body-temperature may still range slightly above the normal. Then once more, and perhaps over and over again, fever with all the former symptoms gradually returns; and now, if it has not declared itself before, the peculiar fleeting rheumatic-like affection of the joints or fasciæ, so characteristic of the disease, shows itself in a large proportion of cases. One day a knee is hot, swollen, and tender; next day this joint may be well but another joint is affected; and so this metastatic, rheumatic-like condition may go on until nearly all the joints of the body have been involved one after the other. The patient may suffer also from neuralgia in different nerves—intercostal, sciatic, and so on. Orchitis is an occa-

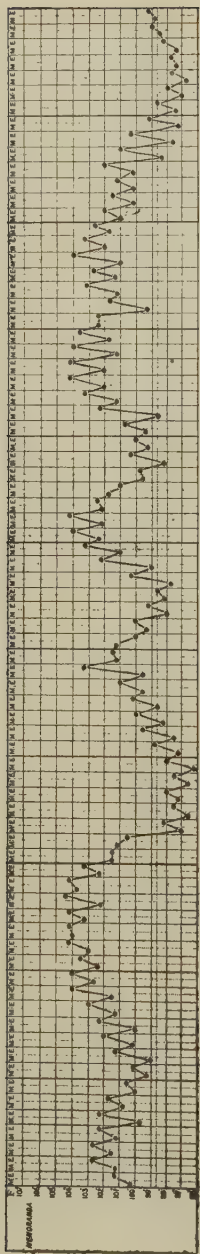


Chart 17.—Undulant fever: typical case. (By permission of London School of Hyg. and Trop. Med.)

sional early complication, and may be mistaken for testicular mumps. In some cases these complications are severe and characteristic; in others they may be mild, or absent altogether. In this respect the same infinite variety exists as in other specific fevers. In severe cases a purpuric condition with bleeding from the gums is occasionally observed. Epistaxis may occur.

The most characteristic feature of undulant fever is the peculiar behaviour of the temperature (Chart 17). In a mild case there may be a gradual ladder-like rise through a week or ten days to 103° or 104° F., and then through another week or so a gradual ladder-like fall to normal, the fever, which is of a continued or slightly remitting type, leaving for good without complication of any sort in about three weeks. Such mild cases are the exception. Usually, after a few days of apyrexia, absolute or relative, the fever wakes up again and runs a similar course, the relapse being in its turn followed by an interval of apyrexia, which is again followed by another relapse; and so on during several months. This is the "undulant" type from which Hughes derived the name he suggested for the disease—*febris undulans*. A factor of practical importance from the diagnostic point of view is the tendency for the fastigium of the temperature curve to occur towards mid-day, or early afternoon (generally about 2 P.M.), a feature by which it may be distinguished from enteric, in which the maximum rise generally occurs towards 6 P.M., or from other long-continued septic fevers, such as that in hepatic abscess, in which this takes place towards night-time.

In cases of another class a continued fever persists for one, two, or more months,

with or without the usual rheumatic, sudoral, and other concomitants—the “continued” type of Hughes.

Usually remittent or nearly continued in type, in a proportion of instances (generally paramelitensis infections) the fever exhibits distinct daily intermissions, the swinging temperature chart suggesting sepsis or malaria. But there is no local evidence of suppuration; the malaria parasite cannot be discovered in the blood, the quotidian rise of temperature is accompanied by no ague-like rigor, or at most only by a feeling of chilliness, nor is the disease amenable to quinine. This is the “intermittent” type of Hughes. In other instances these types may be variously blended.

In some patients, two to three months may elapse before they are finally rid of the tendency to febrile attacks and characteristic pains and aches. According to Bassett-Smith, the average duration of the disease is four months, but may be two years. The shortest period is about three weeks.

As in other zymotic diseases, cases of all degrees of severity are met with in undulant fever. Bassett-Smith recognizes five types:

(a) *Ambulant*.—The patients have no symptoms, but are excreting *Br. melitensis* in their urine and are naturally potential sources of infection.

(b) *Mild cases*.—These last about a fortnight and are apt to be mistaken for paratyphoid.

(c) *The ordinary type*.

(d) *The malignant type*, with hyperpyrexia and toxæmia. This is usually fatal, and considerable difficulty may be experienced in making a diagnosis, as in the case reported by Archibald in which death took place on the twenty-seventh day.

(e) *An intermittent type* with hectic fever, sweats, and general wasting. This is liable to be mistaken for tuberculosis, and appears to be common in South Africa.

Complications and sequelæ.—As a rule, by far the most serious consequences of undulant fever are the debility it entails, the emaciation, the profound anæmia, the rheumatic-like pains, the neuralgias, and such sequelæ as abscess, orchitis, mastitis, parotitis, boils, etc. It is prone to give rise to ovarian pains, dysmenorrhœa, amenorrhœa, menorrhagia, and to favour abortion and premature labour. In the male, intermittent hæmorrhages from the urethra are not uncommon. The germ may pass into the foetus; children born in such circumstances are weakly.

Complications such as splenic and hepatic enlargement, enlargement of the mesenteric and cervical glands, suppuration, phlebitis, chorea, various psychoses, arteritis, endocarditis, melæna, hæma-

turia, etc., are met with occasionally during the long course of this disease. When death occurs it is usually from suddenly developed hyperpyrexia ; occasionally it is brought about by exhaustion, by hæmorrhages and purpuric conditions, or by some pulmonary complication such as pneumonia. In a few instances the fever is a fulminating type, rapidly ending in death from hyperpyrexia.

After such a long, debilitating illness the susceptibility to tuberculosis is much enhanced.

Bruce holds that one attack confers immunity ; other authorities believe that one attack actually predisposes to subsequent attack. The latter is Bassett-Smith's opinion, based on the fact that he finds the bactericidal power of the serum and the phagocytic energy of the leucocytes lowered during, and for some considerable time after, an attack.

Prognosis.—As a general rule, in military and naval forces the mortality-rate is low, from 2 to 6 per cent., but in the civilian population it may be considerably higher. Death may occur from hyperpyrexia, heart-failure, or pulmonary complications. Bassett-Smith points out that a persistent temperature of 104° F. may indicate a grave prognosis, as may also an intermittent pulse. Alarming symptoms may develop at any stage of the disease, especially in relapses. Though it may be unwise to forecast how long a fever may last, yet when the pyrexia has subsided for more than ten days, and the patient's tongue is clean and his appetite good, no further relapses may be expected.

Treatment.—When the diagnosis is sure it is well to give a purge—none better than calomel and jalap—and to instruct the attendants to keep the patient's temperature systematically below 103° F. by cold sponging with vinegar and water or, if necessary, by cold bath or by ice variously applied. In view of the prolonged nature of the fever this measure is one of importance ; at the same time, such treatment need not be applied too energetically, or so as to depress : a fall of 2° or 3° is all that is desirable.

Bassett-Smith recommends yeast and its products, in order to stimulate leucocytosis. Quinine and, on account of the joint affection, the salicylates are very generally prescribed ; both are useless, if not injurious. Phenacetin and similar antipyretics are also often given to bring down temperature ; but the wisdom of employing depressing drugs in so chronic and asthenic a disease is, to say the least, questionable. Threat of hyperpyrexia is best met by early employment of sponging, the wet pack, or, if necessary, the cold bath. Sleeplessness may demand hypnotics, such as trional and sulphonal ; headache, if severe, moderate doses of

phenacetin, pyramidon, or a similar drug; inflamed joints or testes, the usual local applications; constipation, enemata or aperients. In fact, the treatment resolves itself into a treatment of symptoms.

The intravenous injection of various metallic compounds in undulant fever with a view to cutting the fever short is under trial. The injection of mercurochrome 220, in doses of 0.22 gm., has been tried, apparently with favourable results. The subsequent reaction may be severe (*see* p. 257). The intravenous injection of collargol, 2-4 c.c. of a 10-per-cent. solution, is advocated by Ziemann, while injections of argochrom—a combination of silver with methylene blue, has been recommended by Nocht in doses of 0.2 gm. on from three to seven occasions, with three-day intervals; it can also be given as a rectal enema in the same doses as above. Intravenous injections of neosalvarsan are said to be useful occasionally.

Vaccine-therapy.—The therapeutic use of vaccines of dead organisms, prepared and administered according to Wright's methods, has been favourably reported on.

Autogenous vaccine.—In the Editor's experience, stock vaccines are of little benefit. The vaccine should be autogenous and prepared from the patient's organism isolated from blood-culture. In the latter instance, as a general rule, a considerable local reaction develops at the site of injection. In these cases where blood-culture has been successful the initial dose should be 50,000,000 organisms, and it should be progressively increased at three-day intervals, up to 200,000,000. In intractable cases the administration of vaccine in this manner certainly results in the lowering of temperature and in the clinical improvement of the patient's condition. Occasionally a pooled vaccine made from several different strains produces better results than does an autogenous one.

Serum-therapy.—Sergent and Lhéritier have produced an anti-melitensis serum by intravenous inoculation of cultures into a horse. They say it is effective if given in doses of 50 c.c. on three consecutive days. It is useful in chronic as well as in acute cases.

The *diet* at first should consist of milk (in Malta, boiled); later, of broths and eggs and, if necessary, stimulants. Solids must not be freely given during high fever or when the tongue is coated. If appetite is present, ordinary simple food may be taken. Lemonade or lime-juice should be given after a time; not merely as a pleasant, thirst-relieving beverage, but with a view to averting scurvy—not at all an improbable complication if the dietary be too restricted over a long period. Feeding must be conducted with the greatest circumspection, avoiding overfeeding on the one hand and a low

monotonous diet on the other. The tongue and the appetite are the best guides.

Exercise, travelling, and anything that tends to induce fatigue are prone to provoke relapse if indulged in prematurely; but a couch or chair in the garden is to be encouraged, weather permitting. The patient should rest for at least three weeks after the temperature has become normal.

Flannel clothing should be worn, and frequently changed if there is much sweating.

When possible, the subject of undulant fever would do well to avoid the endemic area for one or more years after recovery. In chronic cases a change of climate would appear to be the only therapeutic measure of value.

Prophylaxis.—Malta and those Mediterranean ports in which this fever is endemic should be avoided by pleasure- and health-seekers during the summer. Those who are obliged to live there all the year round would do well, at this season, to leave the towns and reside in places of healthy repute in the country. As a matter of precaution, in the endemic areas the drinking-water, food, and drains ought at all seasons to receive special attention. *All milk should be avoided, or sterilized by boiling*, and food dishes should be washed with boiled water. Every care should be taken to avoid insect-bites and other skin lesions. Laboratory workers must be careful in handling cultures of the bacterium; the accidental introduction of the organism into the conjunctival sac has sufficed to cause the disease.

The discovery that goat's milk is the principal medium through which undulant fever is communicated to man has led to very striking and important results. Unfermented cheese is a frequent source of infection and should be prevented. In Toulon the disease has been traced to "fromage cervelle" made from the milk of sheep and goats. Prophylactic measures should therefore be based on the considerations that epidemic abortion in cattle and undulant fever in man may be closely connected.

On the recommendation of the Mediterranean Fever Commission, the use of the milk of the Maltese goat was interdicted for the naval and military forces of that island. Immediately the incidence of undulant fever began to drop—in the Navy, from an average of 240 per annum up to 1916, to 3 in 1910, and in the Army, from a previous average of 315 per annum to 9 in 1907. In 1909 the health authorities in Malta were authorized to kill all goats whose blood or milk gave the *Brucella melitensis* reaction. The goat population of the island was consequently reduced from 17,110 in 1907 to 7,619 in 1910. Concurrently the fever incidence in the civil population fell from an annual average of 632 to 318 (Eyre). At present, consequent upon

the issue of condensed milk in place of goats' milk, undulant fever has almost disappeared from Malta (Stephens).

These facts suffice to indicate the direction preventive measures should take. It must be borne in mind that certain products of milk—cheese, butter, etc.—may communicate the germ, and, further, that infected goats may appear to be in perfect health and may milk satisfactorily.

The prevalence of infected animals is best determined by cultivating the organism from their blood or milk; failing this, serum reactions (p. 274) and Zammit's test are employed. The latter, which is known as the *lacto-reaction*, consists in diluting the milk to 1:20 and mixing it with a dense emulsion of *B. melitensis* or *paramelitensis*. The mixture is drawn up into a capillary tube and placed in the incubator for twenty-four hours, when any sedimentation present may be detected. It is better to heat the milk first to 56° C. for half-an-hour.

The proportion of infected goats has been estimated as follows :—

Malta	50	per cent.
Algeria	3·4	„ „
Tunis	30·7	„ „
Marseilles	34·2	„ „

Prophylactic inoculation.—Nicolle and Conseil conducted some experiments on man which seem to show that it is possible to immunize against undulant fever by subcutaneous injections of killed cultures of the organism, and similar results were obtained by giving 100,000,000 organisms by the mouth on three consecutive days, and again on the fifteenth day. These results were controlled by subsequently injecting cultures of living organisms; the controls in both cases developed undulant fever.

CHAPTER XV

FEVERS OF THE ENTERIC GROUP

THE enteric group of fevers includes typhoid fever, due to *Bacillus typhosus*, and the paratyphoid fevers, due mainly to *B. paratyphosus-A* and *B. paratyphosus-B*.

The term enterica has been used for both typhoid and paratyphoid infections.

History.—In the earlier half of the nineteenth century, typhoid and typhus fever were grouped together under the term “continued fever.” The first clear differentiation of typhoid from typhus on clinical and pathological grounds resulted from the work of Murchison and Jenner (1855–62). Then came the discovery of the *Bacillus typhosus* by Eberth in 1881, followed by that of *B. paratyphosus-A* (Brion and Kayser), of *B. paratyphosus-B* (Schottmüller), and of *B. paratyphosus-C* (Hirschfeld, 1919).

Geographical distribution.—Besides being the scourge of the young European in India, enteric is common enough in Japan, in China, in Cochin China, in the Philippines, in the Malay country, in Mauritius, in West and South Africa, in Algeria, and, in fact, wherever it has been properly looked for. Thanks to protective inoculation with the triple vaccine (T.A.B.) and to sanitary measures, enteric fever during the Great War was no longer the chief disease in our armies.

Prevalence.—Enteric fever is prevalent among young soldiers and recently-arrived civilians in the East, but, fortunately, liability to infection decreases with length of residence, due apparently to a kind of acclimatization. The well-known immunity of native races to typhoid is probably due either to mild attacks of the disease in childhood or to the immunizing effect of living in constant contact with typhoid infection. In insanitary native cities—Chinese, for example—where the European would almost surely contract typhoid, the natives have acquired a high degree of immunity. The typhoid and paratyphoid infections among Europeans in the tropics appear to be more virulent, and to cause a death-rate twice as heavy as that commonly observed in England. Accord-

ing to English statistics, the death-rate is given as about 1:8 attacked, but in India only recently the death-rate is stated as rather over 1:3.

Up to the early days of this century, typhoid in India used to kill more European soldiers than did cholera. Enteric fevers are apt to occur in camps in localities previously unoccupied by man. This has long been noted in India, while in Australia typhoid has occurred in the back country many hundreds of miles from human habitations. These observations have suggested that the typhoid bacillus may exist as a virulent saprophyte under certain conditions of soil and temperature.

Epidemiology and endemiology.—Practically the essential factor in the propagation of enteric fevers in the tropics, as in temperate climates, is the individual who is passing enteric bacilli in his urine or fæces, or in both. He may be in the acute or the convalescent stage, or a "carrier." Three kinds of enteric carriers are alluded to by writers on this subject: (a) The *acute carrier*, who passes enteric bacilli in the excreta for a short period after an attack of enteric fever. (b) The *chronic carrier*, who continues to pass enteric bacilli in the excreta for years, possibly permanently. Chronic carriers are more often women than men. The gall-bladder being the seat of a chronic infection, the carrier sometimes suffers from gall-stones and cholecystitis. (c) It is believed by some that a person may pass enteric bacilli in the excreta without having at any time previously suffered from an attack of enteric fever. Such a person is called a *passive carrier*.

The enteric carrier is a danger to the community, the degree of danger depending to some extent on his personal hygiene, but much more on the sanitary condition of the locality. Under an efficient water-carriage system of sewage disposal there is a minimum risk of the carrier conveying infection. Where the conservancy system—i.e. the dry closet—is employed, as in the tropics generally, the risk of infection is great. The modes of infection are: (1) directly from the infected person (patient or carrier) to the susceptible; (2) indirectly through water supply; and (3) indirectly by fly-carriage and contamination of food.

B. typhosus is practically world-wide in its distribution. Paratyphoid-A fever is the most common form of the infection in the East (India, etc.), paratyphoid-B fever in Europe. During the Great War the majority of enteric infections in France were paratyphoid-B. The most extensive enteric epidemic occurring in the British and French troops was on the Gallipoli peninsula in 1915. But, relatively to what had happened in former campaigns, the cases of typhoid

in this epidemic were few, the armies being almost completely protected by antityphoid inoculation. In the earlier part of the epidemic, paratyphoid-B was the prevailing infection, while in the later phases the cases were almost exclusively paratyphoid-A. Paratyphoid-C fever, which is probably identical with the fever caused by *B. aertrycke*, is widespread in British Guiana, but elsewhere has probably not the epidemiological importance of the other three fevers (Giglioli).

Etiology.—*Description of organisms.*—*B. typhosus* is a Gram-negative motile rod, 2–4 μ in length and 0.5 μ in thickness. It is provided with numerous peritrichous flagella, and is very active when grown on artificial media. On these it thrives well, with growth resembling that of *B. coli*, but less dense. In its biochemical reactions it differs considerably from that organism, and produces acid without gas-formation in maltose, glucose, and mannite, but causes no change in lactose, saccharose, and dulcitol. It produces slight acidity in milk without clotting. No indol is produced in peptone water (see Table, p. 382). The paratyphoid bacilli A, B, and C resemble in their general morphological characters and staining reactions *B. typhosus*, but differ from it in their biochemical and immunity reactions. They also, like *B. typhosus*, are non-lactose-fermentors, but produce acid and gas in glucose, mannite, maltose, and dulcitol, though they do not affect saccharose nor form indol in peptone water. The “A” bacillus is weaker in fermentative power than “B,” and it produces permanent acidity in litmus milk, whilst “B” first produces acid, returning later to a permanent alkaline reaction. Their immunity reactions are also quite specific. The “C” bacillus differs from “B” in its immunity reactions only, and some bacteriologists might prefer to call it a serological race of “B.”

The portal of entry of the enteric bacilli into the tissues of their host would appear to be the lymphoid masses forming the Peyer’s patches and solitary follicles of the ileum. Here they cause a hyperplasia of the lymphoid tissues, followed at a later stage, in severe cases, by necrosis, sloughing, and ulceration. The bacilli pass on to the lymphatic glands of the mesentery and posterior abdomen, which become enlarged. Finally they enter the blood-stream. The period of bacillæmia coincides with the early febrile stage of the disease, and appropriate hæmoculture is successful in the majority of cases in which it is undertaken sufficiently early—i.e. while the temperature is still rising, or when it is continued without marked remissions. It is seldom successful after the first marked morning remission, especially in paratyphoid fever, or after lysis has commenced. The duration of bacillæmia varies greatly, depending on the severity of the case and duration of the pyrexia. It is, on an average, longer in typhoid than in the paratyphoid fevers. It is important, therefore, in the diagnosis of enteric fever, to set about hæmoculture as early as possible; every day’s delay diminishes the chance of success.

It has been suggested that in enteric infections the invading organisms enter the blood-stream first (possibly through the tonsils), and that the intestinal lesions are secondary to the bacillæmia.

Although bacilli are eliminated in the fæces and urine, it is only in a small proportion of cases that they can be isolated from the excreta, even on repeated examinations.

Pathology.—The most striking lesions found post mortem (in addition to the tissue changes common to all continued fevers) are :

Ulceration of the intestine, especially the Peyer's patches and solitary follicles in the ileum and jejunum ; enlargement and congestion of the abdominal lymphatics ; and enlargement and congestion of the spleen.

The most notable differences in the post-mortem appearances between typhoid and the paratyphoid fever are :

In paratyphoid fevers the intestines more frequently show no change ; in paratyphoid fevers the intestines may be acutely inflamed throughout their length, the lymphatic tissue escaping ; and in paratyphoid fevers ulceration of the large intestine is relatively more frequent.

Post-mortem bacteriology.—The causative organism in enteric fevers may be recovered post mortem from the intestinal lesions, the enlarged abdominal lymphatics, the spleen, the gall-bladder, the heart's blood, and other tissues of the body.

Symptoms.—The usual *incubation period* for all the enteric infections is about fourteen days, but it may be shorter than seven or longer than twenty-one days.

There is a wide range in the severity of the infections, and it will be readily understood that one clinical description cannot apply equally to all cases, from the mildest to the most severe. Moreover, the variation is more in the degree than in the nature of the clinical manifestations. After all that has been written, especially during the Great War, on "atypical" enteric fever, this group remains, whether in inoculated or uninoculated patients, remarkably true to one type—which may be termed the "enteric type."

The typical *onset* is a gradual one, but it may, especially in paratyphoid fever, be sudden, with a shiver or even a rigor. Head-ache is the most constant early symptom, and is usually accompanied by malaise, anorexia, pains throughout the body and limbs, and insomnia. The tongue is coated, the mouth dry and uncomfortable, and the patient thirsty. There is a characteristic moist facies with cheek-flush, and a general apathy. These symptoms vary greatly, and in the mildest cases may pass undetected. Epistaxis is more common in typhoid than in paratyphoid. There may be pain or general uneasiness in the abdomen, but in mild paratyphoids the patient in many cases does not refer to that region. There may be diarrhoea from the commencement, or diarrhoea followed in a few days by constipation, or the patient may have obstinate constipation from the beginning. The temperature is invariably raised. It may mount stepladder-like during the first week, or it may rise suddenly, to reach its highest point in the first 24–28 hours, and, after a period of continued fever, begin to remit in the morning and terminate by lysis. A highly

characteristic feature of all the enteric infections is the pulse, which is usually soft, often dicrotic, and relatively slow. (Charts 18-22.)

On physical examination, the abdomen may be found to be more or less distended, as in severe typhoid, or there may be little or no distension, as in the majority of paratyphoids. Splenic enlargement is practically a constant feature, the organ usually enlarging sufficiently to render, at some stages of the illness, its lower pole palpable below the left costal margin. It may be felt in some cases on the second or third day, if the patient comes under observation so early, or it may not be palpable till the second or third week, or even later. In some cases it becomes palpable for the first

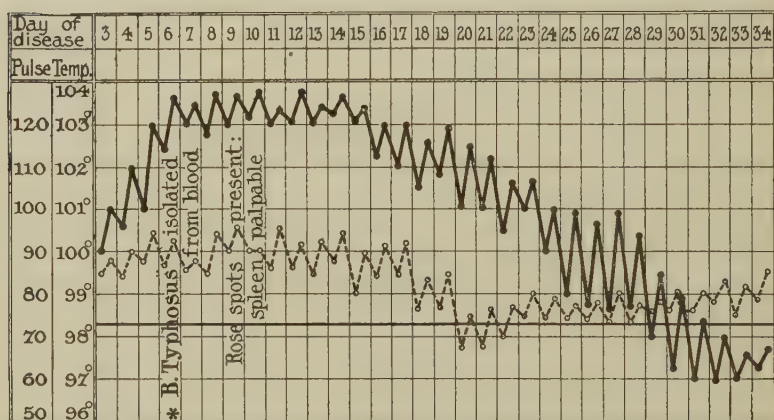


Chart 18.—Typhoid fever, with graph of pulse-rate. (Garrow.)

time only after the temperature has become normal. Usually about the seventh to the tenth day, but it may be earlier or much later, "rose spots" appear. These vary considerably in number, size, shape, general characters, and distribution. There may be only two or three on the abdomen, or the body and limbs may be covered, from the soles of the feet to the scalp. They are of a pale-rose colour, slightly raised, round or lenticular, and fade on pressure. The more profuse eruptions occur in paratyphoid fever, especially paratyphoid-A. When the eruption is not of this profuse type its distribution is characteristic: 90 per cent. or more of it is on the trunk, between the levels of the iliac crests and the nipples. The patient usually coughs and has a certain degree of bronchitis.

Clinical diagnosis.—In the literature of enteric there is frequent reference to mild, atypical, abortive, and clinically unrecognizable forms; and it appears to have become the custom to leave

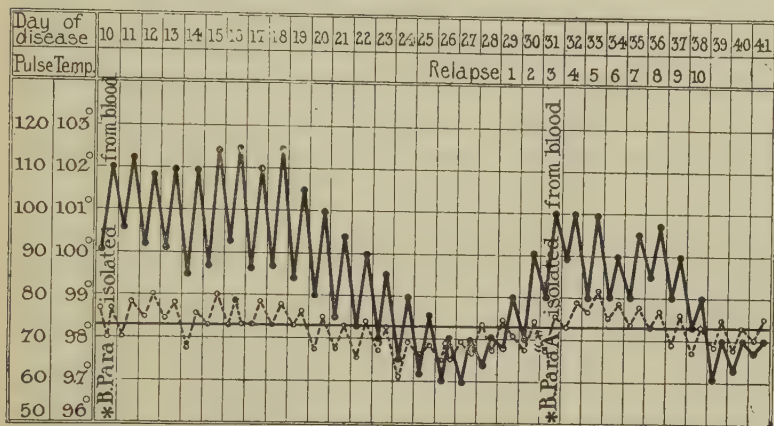


Chart 19.—Paratyphoid-A fever, with graph of pulse-rate. (*Garrow.*)

the question of diagnosis to the laboratory. This was particularly so during the Great War, both at home and abroad, and it is greatly to be deprecated, because careful and repeated clinical scrutiny of

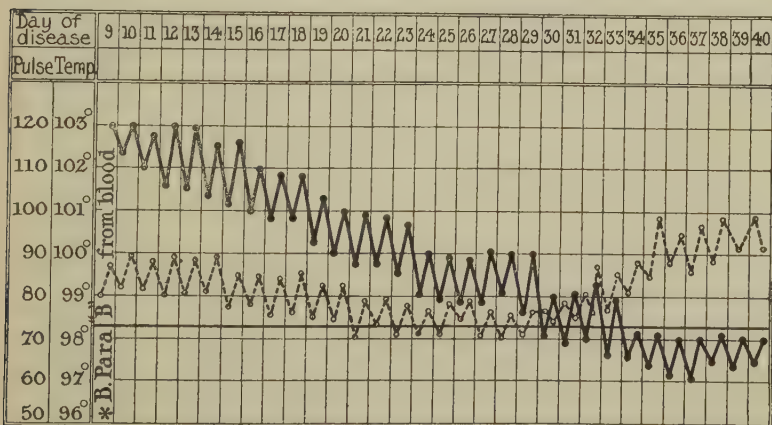


Chart 20.—Paratyphoid-B fever, with graph of pulse-rate. (*Garrow.*)

these cases is more than ever necessary. It is Garrow's opinion that the great majority can be correctly diagnosed clinically. While laboratory methods of diagnosis in the enteric group are un-

doubtedly important, undue value has been attached to certain bacteriological and serological findings, even to the extent of creating new clinical types of the disease to correspond to them. Far from being protean in their clinical manifestations, the enteric fevers are remarkably constant and true to type. The cardinal signs are five in number :

(1) Compound pyrexia of remittent type ending by lysis; (2) low pulse-temperature ratio; (3) characteristic toxæmia; (4) splenic enlargement; (5) eruption of rose spots. It is not pretended that this list exhausts the diagnostic signs and symptoms; but a

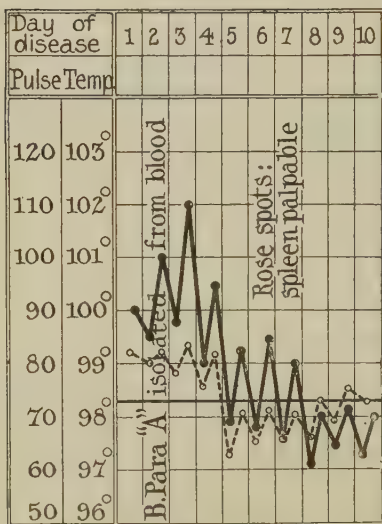


Chart 21.—Anomalous paratyphoid-A fever. (Garrow.)

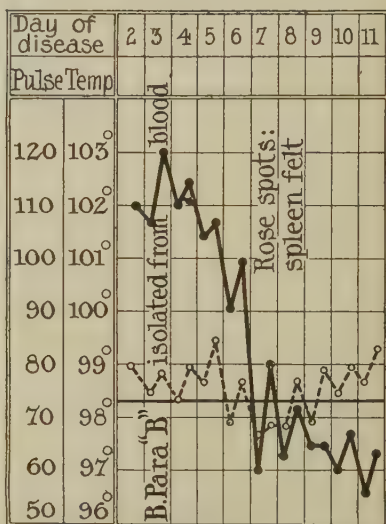


Chart 22.—Anomalous paratyphoid-B fever. (Garrow.)

consideration of these five signs will, in the great majority even of the milder cases, lead to correct diagnosis.

(1) *Pyrexia*.—Continued pyrexia of remittent type, ending by lysis, may be regarded as a feature of every case of acute enteric fever (typhoid or paratyphoid). The pyrexia may be high or low, long or short, with remissions great or small. The onset of pyrexia may be gradual or sudden, and lysis may be slow or rapid, thus giving a great variety of temperature charts within the type; but there is no good evidence to show that the fever ever departs from this type. *Cases presenting the following features certainly should not be regarded as enteric:*

- (a) Temperature is normal or subnormal throughout the entire illness ("apyrexial type of enteric").
- (b) Temperature reaches normal or subnormal at some period of the twenty-four hours on every day of the illness ("intermittent type of enteric").
- (c) Temperature shows perfect tertian or quartan periodicity throughout ("malarial type of enteric").
- (d) Temperature shows a series of short relapses of one to three days' duration, occurring at intervals of a few days ("trench-fever type of enteric").
- (e) The temperature ends by a genuine crisis.

Examples of all these so-called "types of enteric fever" will be found in the literature, the erroneous diagnosis having been based upon some unwarrantable bacteriological or serological finding.

(2) *Low pulse-temperature ratio*.—One of the most valuable diagnostic points is the slowness of the pulse in relation to the pyrexia. The normal pulse-temperature ratio may be tabulated as follows:—

Pulse . . .	50	60	70	80	90	100	110	120	130	140
Temperature .	96°	97°	98°	99°	100°	101°	102°	103°	104°	105°

In enteric fever the pulse is, as a rule, 20 or 30 or 40 beats per minute slower than thus indicated. For example, it is common to find an enteric patient with a temperature ranging about 103° to 104° F., and a pulse of 90 beats per minute, or it may be even slower. If the pulse is recorded graphically in red ink alongside the temperature curve in black, a very striking clinical feature of great diagnostic significance is clearly brought out.

(3) *Characteristic toxæmia*.—There is something very characteristic in the general appearance, facies, and decubitus of the enteric-fever patient. The disease may in many cases be confidently diagnosed by a glance at him as he lies in bed. He has a dull, heavy, toxin-laden appearance in the early acute stage of his disease, with a moist face and flushed cheeks. The experienced clinician at once recognizes the difference between this and the toxæmia of, say, malaria or relapsing fever. In the mildest paratyphoid infections there is little or nothing of this toxæmic appearance, and some infections other than enteric are accompanied by a general toxæmia closely resembling that of enteric fever. Nevertheless, this sign to the experienced physician, when taken in conjunction with the others is of great diagnostic significance.

(4) *Splenic enlargement*.—As some degree of splenomegaly is practically an invariable feature of enteric fever, this sign is of considerable value in making a diagnosis. Unlike the majority of tropical splenomegalies from other causes (malaria, kala-azar, etc.), the enlargement is acute, so that, even when superadded to a spleen already enlarged from malaria, it has certain exceptional features of diagnostic significance. For example, the acutely enlarged spleen of enteric is tender. On palpation, the edge of the spleen is seldom more than two fingers' breadth below the costal margin, often not so much; and the enlargement is of comparatively short duration. The spleen may only be palpable for two or three days, and then recede. It may become palpable as early as the second or third day of fever, or not till the second or third week, and it may remain enlarged long into convalescence.

(5) *Rose spots* may appear in the first week, but more often in the second, and tend to come in crops. They may not appear till the temperature is normal. In warm climates, many European skins are apt to show spots more or less like those of enteric fever, as the result of mosquito-bites and of inflammation of hair-follicles, sweat-glands, etc. Great care must be taken in discriminating between the true rose spot and these "pseudo-rose spots." There are many European skins which, in spite of the trying conditions of the tropics, remain free from blemishes of this sort, and in these cases the recognition of rose spots is relatively easy.

Summary of clinical diagnosis.—Every undiagnosed fever in the tropics should be regarded as a possible case of enteric fever and closely observed clinically, at the same time that bacteriological and serological investigations are being carried out and Marris's atropine test is applied. While valuable clinical evidence may be obtained from occasional signs, such as epistaxis, pea-soup stools, abdominal distension, and hæmorrhage from the bowel, the diagnosis should rest in the great majority of cases upon the presence or absence of the five cardinal signs above described. Any case presenting the first, second, and third signs should be treated as enteric (whether the diagnosis is supported by laboratory findings or not) until some other definite diagnosis is arrived at. No case which does not show the first, together with at least two of the remaining four cardinal signs, should be definitely regarded as enteric. Five types of temperature chart have been described, any of which excludes enteric. These, however, imply that the case has had its temperature recorded from the first, which is not often possible. In the majority of cases of active enteric

fever, all five signs are presented at one or other stage of the illness.

Finally, it should be remembered that, for every case of enteric fever which imitates some other disease, there are at least a score of cases of other diseases imitating enteric (malaria, trench fever, phthisis, liver abscess, syphilis, etc.).

Bacteriological diagnosis (see p. 866).—(a) *Hæmoculture* is unquestionably the most satisfactory method of diagnosis; it should be employed, wherever the necessary facilities are available, in every case of undiagnosed pyrexia in the tropics so soon as a blood-film is found to be free from malaria parasites. A successful hæmoculture furnishes the only conclusive evidence that the patient is suffering from active enteric fever, and can hardly be said to be open to fallacy. Unfortunately, however, the usefulness of the method is limited by the short duration of bacillæmia. In many cases which are undoubtedly enteric, negative results are obtained because hæmoculture has been attempted too late.

(b) *Culture of excreta*.—The plating of urine and stools should be undertaken when blood-culture has failed, and should be repeated during convalescence to determine whether the patient is free from infection. This routine method involves much work for relatively few positive findings. Bacilluria occurs generally after the fourteenth day, and in about 15–20 per cent. of the cases, and, as a general rule, cultivation from fæces will only succeed in about 5 per cent. of the cases in which it is attempted. Positive findings from culture of excreta are open to fallacy. The case may be one of an enteric carrier suffering from some illness other than enteric—e.g. malaria, or trench fever. The detection of carriers can only be effectually carried out in a fully-equipped laboratory; at least seven separate and consecutive bacteriological fæcal tests are necessary. These methods are more minutely dealt with in the Appendix.

Serological diagnosis.—One of the simplest and most reliable of laboratory tests is the examination of the blood-serum of suspected enteric-fever patients for the specific agglutinins of the enteric bacilli—the *Widal reaction*. When carefully applied by reliable methods in the case of *uninoculated patients*, it leads to a correct diagnosis in the great majority of cases. Assuming correct technique, the only possible fallacies are that a positive Widal reaction may result from a *previous* attack of enteric, and that a negative result may occur in the early stage of an attack of enteric. If a negative finding is obtained in face of clinical data pointing to enteric, the test should be repeated, on several occasions if necessary. A few cases of enteric, especially paratyphoid-A, may fail to develop agglutinins and continue to give a misleading negative Widal reaction throughout.

The serological diagnosis of the enteric fevers in *inoculated patients* gave rise to much conflict of opinion during the Great War. Inoculation produces in the blood-serum specific agglutinins indistinguishable qualitatively or quantitatively from those produced by infection. The mere recognition of these specific substances therefore has not the diagnostic significance in the inoculated that it has in the uninoculated. It has, indeed, hardly any diagnostic value. It was demonstrated, however, by Dreyer and his co-workers, and by others, that if an accurate estimate of the agglutinin content of the serum is made early in enteric fever, and repeated at intervals of a few days, there is a steady rise to a maximum, followed by a slower fall. Dreyer and Walker stated that this maximum usually occurred between the eighteenth and twenty-first day of the illness, and almost invariably between the sixteenth and twenty-fourth day. They therefore gave to the latter period the name "period of expectation." To this agglutinin fluctuation they attached a significance practically pathognomonic. Unfortunately, their claims are not borne out by the published cases. While the method is undoubtedly of value, the results obtained are often very difficult to interpret, and misleading. Some undoubted cases of enteric fail to give this fluctuation, while some cases of fevers shown conclusively not to be enteric give a characteristic rise and fall in the inoculation agglutinins. The truth probably is that the majority of enterics give a fluctuation and the majority of fevers not enteric do not. Thus the agglutinin fluctuation, when considered in relation to the clinical data, though useful, should not in itself be regarded as conclusive.

Atropine test.—This test, devised by Marris, depends on the fact that in health or disease, other than enteric, a hypodermic injection of atropine sulphate ($\frac{1}{32}$ gr.) is followed by a rise in the pulse-rate amounting to at least 15 beats per minute, whereas in enteric no such rise follows. Should there be any rise at all, it will be less than 14 beats per minute, but often there is none.

In the application of the test the patient should lie horizontally and remain at perfect rest. He should not be tested till at least one hour has elapsed since the last meal. The pulse-rate should be counted for at least ten minutes, and then $\frac{1}{32}$ gr. of atropine should be injected over the triceps region. After an interval of twenty-five minutes the pulse should be counted again, minute by minute, until it is clear that any rise which may have followed the injection has begun to pass off. The period of the disease during which the test is most reliable is said to be the fifth day to the end of the second week.

Auxiliary methods of diagnosis.—The diazo-reaction is useful, but may be present in malaria. Russo's methylene-blue test is said to be more conclusive, as it is absent in malaria.

Differential diagnosis.—A careful, systematic physical examination of every organ and region of the body, together with macroscopic and cultural examination of the blood, sputum, urine, faeces, and other discharges, will furnish evidence of malaria, trypanosomiasis, relapsing fever, pneumonia, tuberculosis, liver abscess, syphilis, malignant disease, worm infection, or other pathological condition. It is only by comprehensive and sustained effort along these lines that the many puzzling pyrexias of tropical countries

can be unravelled and correct diagnosis arrived at. And even when no definite label can be attached, it is often possible to say that the case is not enteric.

The abdominal pain of enteric may be mistaken for *appendicitis*, but the matter may be easily settled by a leucocyte-count, which in the former is a leucopenia with a relative lymphocytosis, and in the latter an active leucocytosis. *Bacillus coli* infections may resemble enteric. *Typhus* is notably difficult to distinguish in its earlier phases; the leucocytosis which is present in that disease will be found of considerable assistance.

It must not be forgotten that enteric fever may coexist with some other acute infection such as malaria.

Diagnosis of typhoid from paratyphoid.—There are no *clinical* features which serve to distinguish the typhoid and paratyphoid infections from one another with any certainty. Yet there are general points in which they differ. Thus, typhoid fever (*B. typhosus* infection) is the most severe fever of the group, with the highest case-mortality (15 per cent. or over, as compared with 2 per cent. or less for the paratyphoid fevers). The typhoid patient looks more toxic; his temperature is, on an average, higher, with smaller morning remissions; he more frequently shows evidence of gross intestinal lesions (ulceration), e.g. diarrhoea, hæmorrhage, abdominal distension, perforation. The rash is more scanty and the individual "rose spots" are smaller and slightly darker than in paratyphoid. There is greater loss of flesh in typhoid than in paratyphoid. Paratyphoid is characterized by a milder toxæmia. There is seldom abdominal pain or distension, and constipation is the rule. Hæmorrhage and perforation are rare. The rash is more profuse and may cover the entire body and limbs.

But typhoid is frequently of the very mild type, and, on the other hand, paratyphoid may be like the worst typhoid. It is therefore quite impossible to say on clinical grounds alone whether any individual case is one of typhoid or paratyphoid.

Still less is it possible to arrive at a differential diagnosis on clinical grounds between "A," "B," and "C" cases of paratyphoid, although here again, over a series of cases, distinct clinical differences can be noticed. For example, relapses in paratyphoid-A are more frequent than in any other of the enteric infections, and less frequent in paratyphoid-B. Paratyphoid-A is, on an average, of longer febrile duration than paratyphoid-B, but the latter, on the other hand, is more often followed by jaundice, thrombosis, and suppurative complications.

Bacteriological.—The most satisfactory differential diagnosis between the different fevers of the group is the isolation of the causative organism from the blood or excreta, and its identification.

Serological.—In uninoculated patients differential diagnosis is obtained by carrying out agglutination tests with the patient's blood-serum against emulsions of the four organisms concerned. Each infection produces its specific agglutinin, and the phenomenon of coagglutination does not often interfere with the diagnosis. In patients who have been inoculated with triple vaccine the problem of differential diagnosis is considerably complicated. The response may be specific, but frequently two or all three agglutinins may show variations:

Treatment.—There is no specific therapy (vaccine or serum) of proved value for enteric fever; nor is there any drug which is known to exercise an active influence over this disease. In these circumstances it is best to confine treatment to providing the best hygienic conditions, good nursing, and careful dieting. All that the great majority of mild paratyphoid cases require is a soap-and-water enema every other day to relieve the constipation. Milk should be the diet while the patient is febrile; thereafter custard, milk pudding, soup, fish, and meat diet. The diet should contain about 70 grm. of protein a day, with a caloric value of 2,500–3,000. Water should be given freely. Purgative medicines should be avoided. The care and cleanliness of the mouth and teeth are important. In cases of great toxicity with high temperature (over 102.5° F.) and no morning remissions, tepid sponging is useful; in the worst cases the cold bath or ice pack may be resorted to. The temperature of the water should be between 70° and 85° F.; a tub of canvas and mackintosh sheeting may be improvised. Food may be given as a stimulant after the bath. The rectal temperature should be taken immediately on removal from the water, and again three-quarters of an hour later. Of late, *vaccine-therapy* has been employed; the homologous organism should be given, subcutaneously or intravenously, in doses of 25–30 millions on each occasion. The injection may be repeated every third day.

The management of convalescence calls for special care, especially in paratyphoid-A infections, and a return to solid diet should be postponed until the temperature has been normal for at least ten days.

For the bacilluria associated with enteric, urotropine (hexamine) in doses of 10 gr. three times a day acts as a specific.

In the event of hæmorrhage, all fluids should be stopped for at least 48 hours, and sufficient morphia injected to keep the patient at rest. A very large amount of blood may be lost without causing a fatal result, so that when feeding is recommenced it

should be proceeded with very carefully. As a general rule, one large hæmorrhage is less serious than a number of smaller ones. When bleeding has ceased, a subcutaneous infusion with saline up to $1\frac{1}{2}$ pints may be permitted, and this may be repeated later should no further hæmorrhage occur. It is advisable, should hæmorrhage be suspected, to give 30 gr. of calcium lactate three times daily; some make a practice of doing so from the sixteenth to the twentieth day of a typhoid fever, and from the fourteenth to the eighteenth day of a paratyphoid. In cases with thrombosis, administration of citrates is indicated.

Prophylaxis.—*Anti-enteric inoculation* is conspicuously successful, as shown by the statistics of the American army, and of the British Army in India. During the Great War the vaccine was modified by the introduction of *B. paratyphosus-A* and *-B*, and the statistics furnish conclusive evidence of the efficacy of this measure of prevention, not only in lessening the incidence, but also in modifying the disease or diseases. Therefore, everybody proceeding from a country like England to the tropics or subtropics should be inoculated with two doses of triple vaccine (T.A.B.), and should be re-inoculated every year subsequently with one dose, so long as he remains in a country where enteric is prevalent.

The typhoid vaccine, as originally introduced, caused a considerable reaction, but by better methods of preparation and dosage in recent years the reaction has been mitigated. The official vaccine contains 1,000 millions of typhoid bacilli, 750 millions of paratyphoid-A, and an equal number of paratyphoid-B, to each c.c. Two doses of 0.5 c.c. and 1 c.c. are given at an interval of ten days. The reaction in the majority of instances is very slight. Occasionally, however, cases of persistent pyrexia with severe local symptoms, malaise, and headache are met with. In countries where paratyphoid-C is prevalent a tetravalent vaccine should be employed.

Preparation of the vaccine.—The organisms are grown upon tryptic agar, washed off in saline and killed by heat. The vaccine is then standardized by combining the various bacterial suspensions in their appropriate proportions. The final emulsion is preserved by the addition of 0.4 per cent. lysol.

Statistics.—During the South African War, when prophylactic inoculation was incompletely practised, there were 60,000 cases of enteric, with 8,227 deaths. With millions of men under arms during the first two years of the Great War, only some 4,000 cases of enteric were reported from France, with a case-mortality of less than 2 per cent. In the Navy, Bassett-Smith's statistics record an incidence of only 144 cases of enteric during the year 1917, of which 8 occurred in inoculated and 136 in uninoculated individuals.

The American army shows much the same figures ; for two years, 1917-19, out of an average strength of over two million men, there were only 213 deaths from enteric, and it is calculated that had typhoid prevailed in the same proportion as in the uninoculated troops in the Spanish-American War the death-roll from this cause would have been over 60,000.

Measures to avoid infection.—The most effective method for avoiding enteric infection is the water-carriage system of sewage-disposal. This, however, is not general in the tropics, so that other methods must be considered. They are: (a) detection of enteric carriers and their control, especially in relation to the selection, distribution, and cooking of food ; (b) protection of water supplies ;

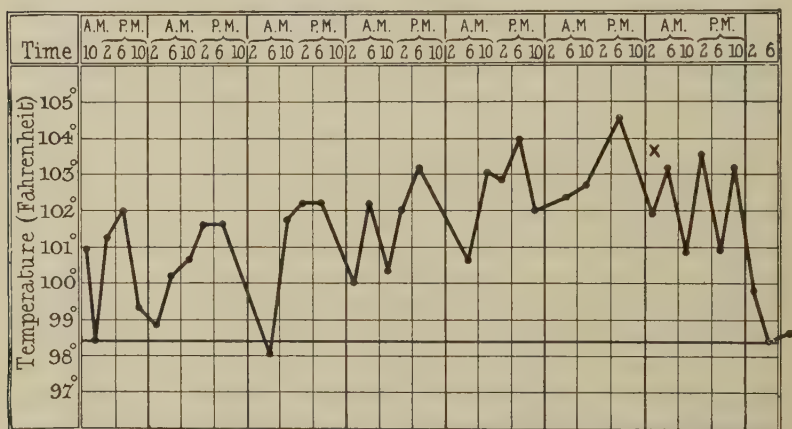


Chart 23.—*B. faecalis alkaligenes* septicæmia. (Bellingham-Smith.)

x Bacillus isolated from blood.

(c) extermination of flies, and preventing them from access to excreta and refuse on the one hand, and to food for human consumption on the other.

ENTERIC-LIKE FEVERS

Septicæmia due to *Bacillus faecalis alkaligenes* and other organisms.—During recent years a series of mild pyrexias, of either remittent or intermittent type, has been proved by Hirst and others to be due to infection with *B. faecalis alkaligenes* (Table, p. 382). It is a common inhabitant of the intestinal canal, where it is not definitely known to exert any pathogenic action. The fever it gives rise to, when present in the blood-stream, may last from two to fifteen days. There is an evening rise with marked morning remission. (Chart 23.) The symptoms resemble those of a mild enteric, the pulse is slow in relation to the temperature, and the tongue is slightly furred. In some cases the patient's serum clumps the homologous organism in a dilution of 1 in 50.

In outbreaks of food-poisoning or "ptomaine poisoning," which occur from time to time, bacilli of the *Salmonella* group, *B. enteritidis* and *B. aertrycke* (*suipestifer*), have been isolated from the blood-stream. The fevers they produce have many features in common with enteric. They differ in the suddenness of the onset with rigors, the accentuation of the gastro-intestinal symptoms, the short duration and rapid termination of the fever. *B. aertrycke* resembles *B. paratyphosus-B* in its biochemical, but may be differentiated from it upon its serological reactions. Giglioli

1



Fig. 61.—Sections of kidney in *B. coli* septicæmia. (Orig.)

1, Aggregation of organisms in intertubular capillaries; 2, large collection of organisms in a medullary vein; 3, passage of bacilli through tubular epithelium of duct of Bellini into lumen.

has recently shown that *B. aertrycke*, or Paratyphoid-C, is widespread in British Guiana and produces there a type of fever which has been mistaken for true typhoid.

Bacillus coli infections.—Infection of the bladder and urinary tract with *B. coli* is frequently met with in both sexes in the tropics. Should the organism enter the blood-stream it may give rise to a prolonged intermittent pyrexia resembling enteric. *B. coli* septicæmia and pyæmia may be a terminal

infection in debilitated natives, especially after bacillary dysentery ; in these cases the organisms gain entrance to the blood-stream through the intestinal lesions, and, becoming arrested in the glomeruli, give rise to multiple minute abscesses in the cortex of the kidneys, from which they escape in an intermittent manner and appear in the urine. (Fig. 61.) The condition is probably much more widespread than has been recognized hitherto, and a series of cases from Egypt has been described by Enright and the Editor. The general condition of the patient, the stupor and the intoxication, may resemble those of enteric, but the onset is generally sudden, with headache, and acute pain referred to both kidney regions. Usually all symptoms of vesical irritation are absent. The tongue is thickly furred ; rigors are numerous and accompanied by profuse sweats. The organism may be recovered in pure culture from the blood-stream during the rigors, as well as from the urine by ureteric catheterization. The acute attacks are liable to be confused with those of malaria. (Chart 24.) The only form of treatment of any avail would appear to be the intravenous injection of 40 c.c. of freshly prepared eusol, diluted with an equal quantity of normal saline solution.

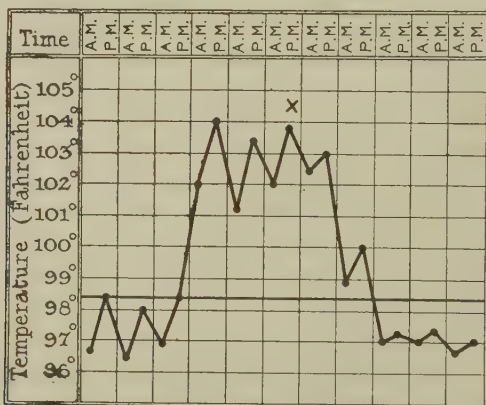


Chart 24.—*B. coli* septicæmia. x *B. coli* isolated from the blood.

Pyelitis.—Owing to the propinquity of the renal pelvis to the colon acute pyelitis due to infection with *B. coli* is very apt to occur, especially in women, in the tropics. The symptoms may commence with a rigor and a dull aching pain in the loins which is increased on pressure. Micturition may be frequent and sometimes a large and tender unilateral mass may be palpated. The results of the inflammation are soon seen in the urine, which contains albumin, pus cells and, sometimes, even blood. *Bacillus coli* is present in large numbers especially in the first specimen of urine passed during the day. Differentiation from malaria, an attack of which it may closely resemble, may be necessary. The treatment should consist of urotropine and acid sodium phosphate alternating with alkalis. Autogenous vaccine treatment with doses of 100 to 200 million organisms would appear to be of distinct benefit. *Cystitis* with pyrexia and acid urine may also be due to *B. coli* and is very apt to occur as a sequel to any debilitating tropical fever, especially in enteric infections. It is always necessary to consider the possibility of this occurrence.

CHAPTER XVI

THE SMALLPOX GROUP

THIS expression, as used here, is not intended to convey that disease of this nature is confined to tropical countries, but rather to emphasize the fact that smallpox, in its various forms, virulent and modified, is a widespread scourge. While not proposing to describe the diagnosis and treatment of smallpox, it is necessary to refer to an aspect of this subject which has come into prominence in tropical medicine during the last few years.

ALASTRIM

Synonyms.—Amaas ; Kaffir Milkpox ; West Indian Modified Smallpox ; Parasmallpox.

Definition.—This disease has been noted by many writers as occurring in the West Indies and South Africa.

The name is derived from the Spanish *alaster*, meaning to scatter or strew over (referring to the distribution of the rash). It is a disease of little or no mortality, and resembles smallpox in its most mitigated form. Indeed, the individual case of this disease is clinically identical with a mild case of smallpox ; the diseases can only be distinguished one from the other in the mass.

Geographical distribution.—This disease has been recorded from the West Indies, South and Central America (especially Brazil), Africa, the Mediterranean area, and during the last 20 years from time to time in Great Britain. The most noteworthy epidemic was the one which occurred in Trinidad in 1902.

Etiology.—Alastrim is very infectious to man, and attacks both sexes : no racial immunity has been observed. The causative organism has not been discovered, though Guarnieri bodies have been described from the lesions. The virus is infective under experimental conditions for monkeys and calves, and produces lesions when inoculated into the cornea of rabbits. The crusts off the pocks are believed to convey the virus of the disease. The infectious agent probably resides in the nasal and buccal secretions at an early stage of the disease. Vaccination is protective against alastrim in a very high degree. This, and the fact that two attacks

may occur in the same individual, are common both to alastrim and to smallpox.

Epidemiology.—A striking difference between classical smallpox and alastrim is seen in the rate of progress through an unvaccinated community. Smallpox becomes rapidly epidemic, whereas alastrim can only be said to “smoulder,” alternately waxing and waning, but never attaining really epidemic proportions. This, no doubt, depends upon the infectivity of the two viruses. There appears to be no seasonal incidence.

The spread of alastrim is brought about by intimate contact and overcrowding.

Pathology.—The lesions are present on the buccal mucous membrane as well as on the skin, and may extend from the palate down the trachea into the bronchi. The actual pocks appear to involve the skin tissues to a degree intermediate between those of chickenpox and smallpox; they rarely leave any scarring behind.

Symptoms.—The *incubation period* averages about fourteen days; prodromal symptoms may or may not be present. When observed, they are those of an influenza headache, with generalized aches and pains. Severe headache, vomiting, and rigors, typical of the onset of smallpox, are rarely noted. The eruption commences usually on the third or fourth day, but in some cases there is a complete intermission of all symptoms, during which the patient may return to his duties under the impression that he has recovered from an attack of influenza; after the lapse of the quiescent period the eruption appears first on the face and palate, then on the hands and arms, and later on the lower extremities. Thus, in these cases there is a prodromal period of seven or eight days.

Individual lesions.—The papules can be palpated under the skin even before they are visible. As a rule, the eruption appears in one crop, and closely resembles that of smallpox in every respect, any differences being due to the more superficial situation of the pathological process in the skin. The pock may be umbilicated, but collapses more completely on being punctured than does the smallpox pustule, that is to say, it is less definitely multilocular. Drying or crusting begins at about the end of the first week, and crusts have usually fallen by the end of the second or third, at which period the patient is considered to be free from infection.

The rash naturally differs somewhat in appearance (*see* Plate XV) when it occurs on a dark skin; the individual pustules, when ripe and full of pus, show as light creamy-coloured areas, in contrast to the dark purple of the surrounding inflammatory zone, and appear as pearls upon a dark background.



ALASTRIM.

Note patches on inner side of thigh, above knee, around septic cut.

(After L. M. Moody, "*Ann. of Trop. Med. and Parasit.*")

Distribution of the eruption.—This is identical with the distribution of the smallpox eruption, which is centrifugal, and it at once serves to distinguish alastrim from chickenpox, the rash of which has a centripetal distribution.

As in smallpox, the most protected parts of the skin are most free from eruptions, i.e. axillæ, groins, and abdomen. The parts most affected are the face, scalp, shoulders, back, arms, and legs. Any part which has previously been especially exposed to irritation is more profusely affected; thus pocks are apt to cluster at the site of old burns or scars. (Plate XV.)

Confluent rashes may occur, but, though the appearance of the patient is somewhat alarming, his general health appears to be but little disturbed. These cases may be associated with a considerable degree of fever.

It has been noted by most writers on this subject that the fetor accompanying the rash of true smallpox is not present in alastrim.

Prodromal rashes are absent.

The mortality-rate is a minimal one; in the series recorded it is about 0.45 per cent. (Ribas and Moody).

Treatment is symptomatic only; patients should be isolated in a smallpox hospital or elsewhere.

Prophylaxis.—Vaccination offers the most efficient method of protection against this disease, as in smallpox. In spite of the mildness of alastrim, it is considered desirable at present to treat it as a form of smallpox, and not only to isolate patients but to vaccinate contacts.

CHAPTER XVII

HEAT-STROKE

THE term "heat-stroke" conveys the suggestion that heat is the leading etiological factor in the various morbid conditions which custom has grouped under this and similar names.

Heat-exhaustion may occur in any climate, high atmospheric temperature being the essential factor. *Heat-hyperpyrexia* has a peculiar endemicity; while *sun-traumatism* results exclusively from exposure to the direct rays of the sun.

HEAT-EXHAUSTION

Definition.—Sudden faintness, or fainting, brought about by exposure to high atmospheric temperature.

Etiology.—The healthy human body can support with impunity very high atmospheric temperatures. In many parts of the world men live and work out of doors in temperatures of 100° or even of 120° F. The stokers of steamers, especially in the tropics, discharge for hours their arduous duties in a temperature often over 150° F.

When, however, the physiological activities have become impaired, by disease, especially by heart disease, kidney, liver, or brain disease, by malaria, by alcoholic or other excess, by fatigue, by living in overcrowded rooms; or when the body is oppressed by unsuitable clothing; or in the presence of a combination of some of these factors—then high atmospheric temperatures are badly supported, the innervation of the heart may fail, and syncope may ensue.

Symptoms.—When attacked with heat-exhaustion the patient feels giddy, and perhaps staggers and falls. He is pale; his pulse is small, soft, and perhaps fluttering; his breathing is shallow, perhaps sighing, never stertorous; his pupils are dilated; his skin is cold; his temperature is subnormal; and he may be partially, more rarely quite, unconscious. Usually, after a short time, he gradually recovers; very likely with a splitting headache and feelings of prostration. In a small proportion of cases the faint is not recovered from, and death ensues.

Treatment.—In syncopal heat-stroke the patient should be laid at once on his back in a cool, airy, and shaded place. His clothes should be loosened, a little water dashed on his face and chest, and ammonia held to his nostrils. If necessary, a stimulant may be given by the mouth, or injected into the rectum or hypodermically. It is a mistake to douche these cases too freely. The object is rather to stimulate than to depress.

HEAT-HYPERPYREXIA

Synonyms.—Heat-stroke ; Insolation ; Thermic Fever ; Siriasis.

Definition.—An acute condition developing in the presence of high atmospheric temperature, and characterized by sudden incidence of hyperpyrexia, coma, and extreme pulmonary congestion and œdema.

Geographical distribution.—Heat-hyperpyrexia appears to be remarkably restricted. Although this type of disease has been reported as occurring in many countries, on making careful examination it will be found that a large proportion of the reputed cases are really examples of other diseases, more especially of cerebro-spinal fever, apoplexy, tuberculous meningitis, alcoholism, cerebral malaria, or some other phase of acute disease, but not of true heat-hyperpyrexia.

The endemic areas are—in America, the east coast littoral of the United States, more especially in the great towns, the Mississippi valley, the coast of the Gulf of Mexico, the valleys of the Amazon and of the La Plata, and the South Atlantic coast ; in Africa, the valley of the Nile, the coasts of the Red Sea, and a low-lying part of Algeria near Biskra ; in Asia, Syria, Mesopotamia, the valleys of the Indus and Ganges, Lower Burma, Tonquin, and south-east China ; in Australia, the Murray River district, the Queensland coast, and possibly the plains of Sydney. It is not met with on the high seas, although it is well-known on ships in the narrow, land-locked Red Sea and the Persian Gulf. During the Great War dangerous cases occurred most numerous in Mesopotamia, especially during July, 1917, when for three days the temperature reached 122° F. in the shade, and 135° F. in the interior of double fly-tents.

Etiology.—New-comers to the endemic areas and Europeans are more liable than natives or residents of long standing. Men over forty are more susceptible than those of younger age. Apparently, long residence confers a relative although not an absolute immunity.

All ages and both sexes are susceptible ; but in consequence of their habits and more frequent exposure to the predisposing and immediate causes, men are more liable than women.

Heat-hyperpyrexia has generally been attributed to direct action of atmospheric or solar heat on the body. Many theories of the *modus operandi* of this assumed cause have been advanced. Among these may be mentioned superheating of the blood by the

high temperature of the surrounding atmosphere. Most authorities agree that a process of auto-intoxication occurs, as evidenced by the indicanuria. Acetone and diacetic acid occur in the urine of 12 per cent. of cases. Hearne has pointed out that heat-hyperpyrexia is associated with suppression of sweat, which may precede the onset of serious symptoms by 48 hours, for after prolonged exposure to high temperatures the sweat apparatus becomes exhausted and the glands cease to function. With sweating suppressed, the body-temperature tends to adjust itself to that of the atmosphere, but, in view of the increased respiratory and nitrogenous changes, is unable to do so. Coma, delirium, and convulsions appear directly the body-temperature reaches 108° F. Hypodermic injections of atropine have been shown to predispose to heat-hyperpyrexia through its action upon the sweat-glands; and somewhat similar results have been produced in lower animals by Cramer, by injection of β -tetra-hydronaphthylamine, which overstimulates the thyroid-adrenal apparatus.

Pathology.—A notable feature of fatal hyperpyrexia is the early appearance of rigor mortis. The blood is remarkably fluid, or but feebly clotted. The venous system is loaded, dark fluid blood pouring from the phenomenally engorged lungs and other viscera on section. Both blood and muscles are said to yield an acid reaction more or less pronounced. It has been stated that the red blood-corpuscles are crenated and do not form rouleaux. If the post-mortem examination is made shortly after death and before decomposition changes have set in, the heart in early rigor mortis, particularly the left ventricle, will be found remarkably rigid; this rigidity is sometimes described as being of "wooden hardness." There may be some venous congestion of the meninges, but the brain itself shows no important vascular or naked-eye changes. On microscopic examination, necrotic changes in the ganglion cells, with chromatolysis of the nuclei, are found. The cerebrospinal fluid is clear and under pressure. Cortical changes in the suprarenals have been described. The intestinal mucosa, as well as that of the stomach, is swollen, and exhibits patches of congestion. The temperature of the cadaver continues to rise after death, and may reach 114° F.

Symptoms.—Though sometimes coming on suddenly during exposure to the sun, heat-hyperpyrexia is very often preceded by a distinct prodromal stage. It frequently develops independently of any direct exposure to the sun; not seldom the attack comes on during the night.

Among prodromata, which may show themselves with greater or less distinctness for an hour or two or even for a day or two before the full development of the attack, are great disinclination for exertion, pains in the limbs, drowsiness, vertigo, headache, mental confusion, sighing, anorexia, thirst, intolerance of light—sometimes accompanied by chromatic aberrations of vision—suffused

eyes, nausea and perhaps vomiting, præcordial anxiety, suppression of sweat, urinary irritability, sometimes a sense of impending calamity, an hysterical tendency to weep, and a quickened pulse. The irritability of the bladder is a valuable and easily recognized danger signal. Willcox has drawn attention to the loss of knee-jerks which occurs, and their return is a favourable indication.

The first indication of anything wrong may be a short stage of restlessness, or possibly of wild delirium. This brief preliminary stage rapidly culminates in coma, complete unconsciousness, and high fever, quickly passing into hyperpyrexia which may reach 110° F. The pupils, unless immediately before death when along with the other sphincters they relax, are contracted. The reflexes are partially or wholly in abeyance. There may also be, especially in the graver cases, free watery purging, the dejecta as well as the skin of the patient emitting a peculiar and distinctive mousy odour. The scanty urine may contain blood-corpuscles, albumin, and casts.

Willcox distinguishes different clinical types of heat-hyperpyrexia :

(1) *Gastric type*.—A most deceptive form, in which the axillary temperature is normal, the rectal temperature raised, and gastric symptoms predominate, with congestion of the liver. A fatal hyperpyrexia may develop without previous warning.

(2) *Choleraic type*.—This form is of sudden onset, with purging and general resemblance to true cholera ; it may be fatal within three or four days. The rectal temperature may rise to 110° F. after death.

(3) The *true heat-hyperpyrexia*, in which nervous symptoms predominate, has already been described. It accounts for 70 per cent. of the cases. The temperature may rise to 113° F., and the patient yet recover (Marshall).

Unless active measures to lower temperature are taken early in the progress of the case, and vigorously carried out, in the great majority of instances death will occur within a few hours, or even minutes, of the onset of insensibility. The immediate cause of death is generally the failure of respiration. Rarely do cases linger for a day or two. Partial recovery is sometimes followed by relapse. In favourable cases the disease usually terminates by crisis. Convalescence is rapid. Unless the patient is moved into different surroundings a relapse may occur ; two or even three have been recorded. Occasionally cerebral or cerebellar symptoms may persist.

Usually heat-hyperpyrexia is much more dangerous than ordinary heat-exhaustion, but the death-rate may be materially reduced by early and judicious treatment. In Mesopotamia,

during the Great War, the case-mortality among British troops from this cause was about 8 per cent.

Diagnosis.—The presence of high fever is sufficient to differentiate heat-hyperpyrexia from sudden insensibility caused by uræmia, by diabetic coma, by alcoholic and opium poisoning, and by all similar toxic conditions. Cerebral hæmorrhage, particularly pontine, may, after some hours, be followed by high temperature; but here the febrile condition follows the insensibility, whereas in heat-stroke the febrile condition precedes insensibility. The diagnosis from a cerebral malarial attack may be very difficult; chief reliance has to be placed on the history if obtainable, on the condition of the spleen, and especially on the result of microscopic examination of the blood. Malarial fevers and the early stages of the eruptive fevers in children are very apt to be regarded as heat-stroke, particularly if there has been recent exposure to a hot sun. Cerebro-spinal fever, so often mistaken for heat-hyperpyrexia, may be recognized by the occipital retraction, the irregular pupils, the frequent occurrence of strabismus, Kernig's sign, the comparatively low and fluctuating temperature, the associated herpes, the initial rigor, and its duration.

Treatment.—In all fulminating fevers, including heat-hyperpyrexia, occurring in warm climates, if malaria be suspected, particularly if the parasite be discovered in the blood, quinine should be injected intravenously or intramuscularly at once (7–10 gr. of the bihydrochloride), or given by enema as directed under Malaria (p. 82); this dose should be repeated three or four times at intervals of four hours. In every case of heat-stroke, whether it has been deemed advisable to administer quinine or not, attempts must at once be made to reduce temperature by such rapidly acting measures as the cold bath, or ice applied in various ways to the head and body. Antipyretic drugs are of very little service, even if, in consequence of their depressing action on the heart, they be not actually dangerous; in all serious cases of heat-stroke such drugs must be carefully avoided. The patient should be placed on a wet sheet supported upon bed cradles, thus forming a moist chamber in which he lies; the whole may rest upon a rush-covered bed or “angareeb.” Mackintosh sheets must be avoided. The continuous water-spray with iced water, together with an electric fan, simulates the natural process of sweating to the best advantage. Ice-water enemata are also recommended; to these, should convulsions and restlessness supervene, potassium bromide or chloral may be added. Rubbing the skin with ice, by constricting the capillaries, apparently only obstructs evaporation.

A thermometer should be kept in the rectum, and the application of cold should be discontinued so soon as the thermometer in the rectum has sunk to 104° F., or, in cases of simple thermic fever in which the temperature has not exceeded 106°, when it has fallen to 102°. If powerful antipyretic measures are carried beyond this point the fall of temperature may continue below the normal, even to as low as 91°, and dangerous collapse ensue. In the absence of electric fans an iced wet sheet may be wafted up and down over the patient's abdomen by means of a punkah-like arrangement.

On discontinuance of the iced sheet, the patient should be wrapped in a dry blanket; very likely, perspiration, a favourable sign, will then set in. Stimulants may now be necessary. Strychnine, owing to the marked tendency to convulsions incidental to heat-stroke, must on no account be used as a cardiac stimulant; Chandler, as the result of his large experience, recommended the injection of 40 min. of tincture of digitalis. Convulsions are best controlled by cautious venesection. As death in heat-stroke generally results from failure of respiration, Hearne and others strongly recommend artificial respiration when the breathing threatens to become suspended; it should be maintained for half-an-hour or longer. Lumbar puncture is indicated in cerebral cases as a rational method of relieving intracranial pressure. Intravenous or subcutaneous injections of saline are indicated in the choleraic forms. Gastric cases should receive a liberal supply of bicarbonate of soda—30 gr. every two hours.

During convalescence great care must be exercised to shield the patient from all influences calculated to provoke relapse. The power of sweating may be in abeyance for three weeks or longer.

Prophylaxis.—Patients in hospital are especially liable to develop heat-hyperpyrexia. The most valuable practical method is to attempt to forestall the advent of heat-stroke by periodically inspecting the patients to find out those with commencing suppression of sweat, urinary irritability, restlessness and insomnia.

SUN-TRAUMATISM

In cases of this type, after prolonged exposure to the sun, a febrile condition is established. It is sometimes of great severity, being characterized by intense headache, a rapid full pulse, a pungent dry skin, intolerance of light, sound, and movement, and occasionally by vomiting or delirium, suggesting meningeal congestion. The acute phase may be quickly recovered from, or may prove very persistent and last for days or weeks. It may leave no injurious

effects, or may be followed by a variety of transient or more permanent morbid nervous phenomena.

Etiology.—Manifestly, the symptoms produced are not due to heat, for such effects do not result from exposure to the heat of a furnace, however intense. There appears to be some special element in the solar rays capable of injuriously affecting the tissues, particularly if they have not become gradually habituated to sun-exposure. In this connexion we are forcibly reminded of the phenomena of the actinic rays of the solar spectrum, and of the remarkable tissue changes induced by the Röntgen rays.

Treatment.—Patients suffering from sun-traumatism must be kept as quiet as possible in a cool, airy, and darkened room. The head should be kept shaved, and cold applied to the scalp. The bowels must be free; food should be light and unstimulating, and alcohol in every form strictly forbidden. Restlessness and insomnia are best treated by the bromides. For a considerable time the patient will be troubled with loss of memory, and feebleness of intellectual power and of the faculty of concentration. He may be irritable, liable to headache, and extremely sensitive to heat—more particularly the heat and glare of the sun. So soon as he is able to be removed he must be sent to a cooler climate, and there remain until all trace of his illness has completely disappeared. Indeed, it is questionable if the subject of pronounced sun-traumatism should ever again risk the dangers of a tropical climate; certain it is that he should not return to the tropics so long as the slightest evidence of cerebral trouble remains.

CHAPTER XVIII

THE DIAGNOSIS OF FEVERS IN THE TROPICS

PRECEDING the diagnosis of tropical antecedents, the commoner causes of pyrexia in temperate countries must constantly be kept in mind. At the outset every case should be examined from this standpoint. The possibility of *pulmonary tuberculosis* must always be kept in mind, and not missed because of the presupposition that *any pyrexia in or from a tropical country is necessarily tropical in origin*. (Chart 25.) Secondary and tertiary syphilis, malignant

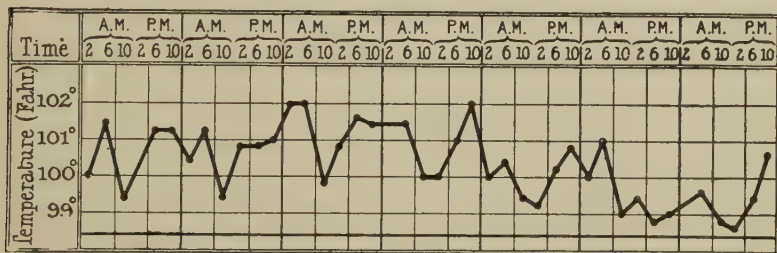


Chart 25.—Miliary tuberculosis. (Dr. G. C. Low.)

endocarditis, suppurative conditions such as empyema, urinary fever, perineal abscess, *B. coli* pyæmia, renal calculus, bacilluria, pyelitis, cholecystitis, malignant disease, and liver abscess, may all give rise to pyrexia of various types. Influenza, again, may occur in world-wide epidemics, and has always to be considered. Fever may also occur in association with helminthiasis, the idiopathic anæmias, as, for instance, pernicious anæmia, spleno-medullary leucocythæmia, and lymphatic leukæmia. A posterior urethritis or prostatitis or ischio-rectal suppuration due to secondary infection with *B. coli* or other organisms may provoke rigors resembling those of malaria. A periodic fever resembling that of malaria or relapsing fever is met with in certain types of lymphadenoma (Pel-Ebstein disease). (Chart 26.)

Malaria.—Much information may be obtained in every case of fever from a simple blood examination; in the first instance this must be directed, in a country in which malaria is endemic, as it

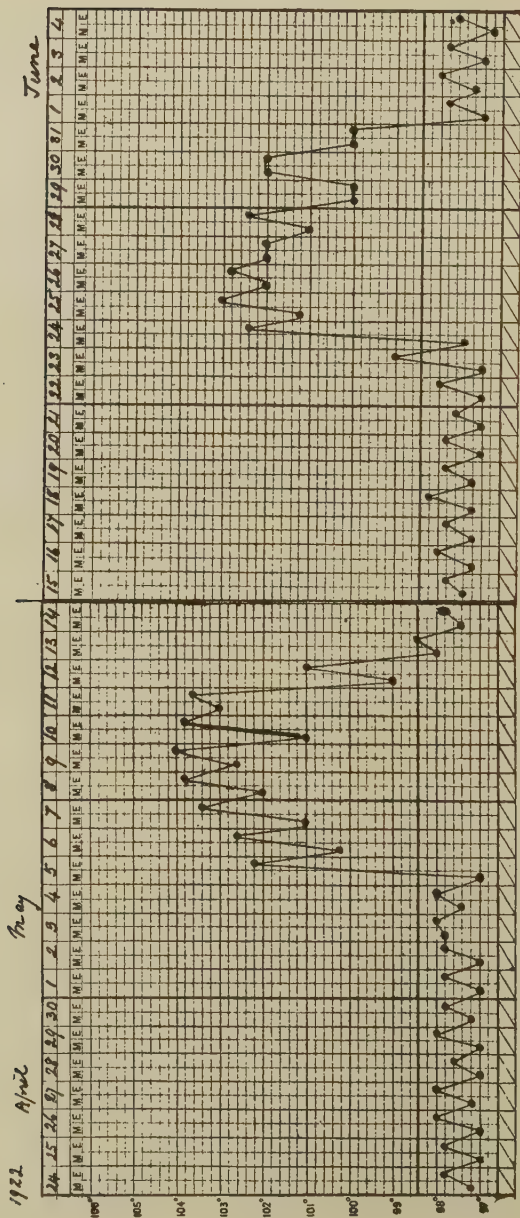


Chart 26.—Pel-Ebstein syndrome, showing typical relapses.

is in most parts of the tropics, towards the discovery of the malaria parasite, always remembering that this parasite often exists as a mere complication, superimposed upon some other infection, such as enteric, undulant, or relapsing fever.

It is advisable to examine the blood before quinine has been exhibited; this applies to all forms of malaria, the benign tertian, subtertian, and quartan, but more especially to the first-named.

There is an idea prevalent that the parasites can be found in the peripheral blood only during the short periods immediately preceding and following the malarial rigor. It is true that they are more abundant at these periods, but it is usually possible to find them in the apyrexial period, especially in the case of the subtertian parasite. In this species the youngest and the most mature forms—the ring and the crescent—are found usually in the peripheral blood, while the remainder of the cycle of the parasite takes place in the internal organs; therefore it is frequently possible to meet with cases presenting the typical clinical appearances (splenomegaly, etc.) in which it is not easy to demonstrate parasites.

On account of the pernicious symptoms which subtertian malaria may exhibit, it is necessary to examine the blood at the earliest possible moment. Even then one should remember that the parasites may only be found after a prolonged search, or, exceptionally, may even be absent entirely from the peripheral blood for thirty-six hours after the onset of fever.

Usually, in the first attack of subtertian malaria, little assistance is obtainable from a study of the temperature chart, as this may closely simulate that of other fevers, especially enteric, though a double rise in the twenty-four hours is suggestive of subtertian malaria. (Chart 27.)

It may be taken as a general rule that in a malarious district a pyrexia, attended by a rigor during the forenoon or early afternoon, is almost invariably of malarial origin, and calls for a blood examination for confirmation. Failing the discovery of the malaria parasite, a considerable rise in the mononuclears as ascertained by a differential count, the absence of any other ascertainable cause, and amenability to quinine-therapy, indicate that the case is of malarial nature.

Relapsing fever.—Another parasite causing fever, and easily detected by simple blood examination, is the spirochæte of relapsing fever (p. 165). It is necessary to bear in mind, in order to confirm the suspicions aroused by the characteristic pyrexia, that these organisms are apt to disappear from, or become very scanty in,

the blood-stream just before the crisis. In other clinical forms, as for instance the relapsing fever of Central Africa and Persia, they may be very scanty, so that a thick-film method may be required to demonstrate them. At the same time, even in the apparent absence of parasites, a considerable polymorphonuclear increase is suggestive of spirochætal disease.

Trypanosomiasis.—The diagnosis of trypanosomiasis need only be considered in the endemic zones of that disease and in travellers who have resided there. It mostly concerns the African, and to a lesser extent the Brazilian form (p. 126). The clinical symptoms—headache, glandular enlargement, and fugitive circinate erythema in the case of *T. gambiense* and *T. rhodesiense*, with noc-

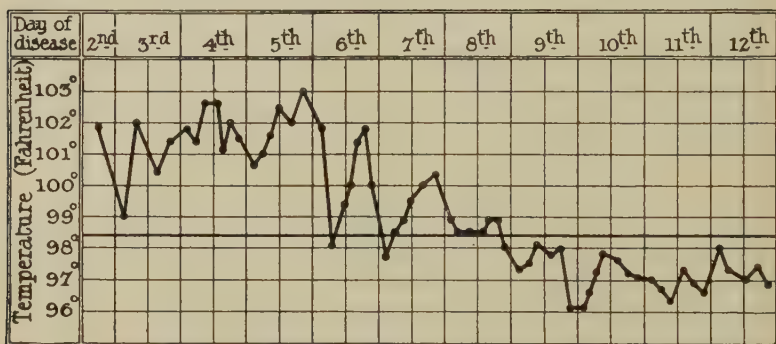


Chart 27.—Subtertian malaria simulating enteric. (Orig.)

turnal pyrexia and headache—should suggest a prolonged search for the trypanosome. This must be done in a thicker film than is usually employed for malaria, and, as these protozoa are scanty in the peripheral circulation, search must be made with a $\frac{1}{8}$ -in. lens, which suffices for their detection. Failing the discovery of the parasite in the blood, gland- and even lumbar-puncture may be resorted to. A persistent increase in the large mononuclear cells, together with a leucopenia and the presence of Kerandel's sign, is suggestive.

Kala-azar.—The diagnosis of kala-azar and its differentiation from chronic malaria is often a matter of considerable difficulty, as the two diseases may coexist. The clinical picture of splenomegaly with hepatic enlargement, a characteristic doubly remitting pyrexia uncontrolled by quinine, anæmia, leucopenia, and a mononuclear rise, should suggest hepatic or splenic puncture as a means of settling the diagnosis. Occasionally the Leishman-

Donovan body may be found in the peripheral blood within the large mononuclear cells.

Infectious jaundice.—The possibility of a pyrexia of otherwise unexplained origin being occasioned by the *Leptospira icterohæmorrhagiæ* must not be lost sight of by the practitioner in the tropics, and the differentiation of infectious jaundice from yellow fever is a matter of considerable difficulty in countries in which the former disease occurs. In a considerable number of cases *L. icterohæmorrhagiæ* may be demonstrated in a blood-film, though it is never abundant; it is more easily found in the urine. Therefore a polymorphonuclear leucocytosis along with grave icterus and splenomegaly should suggest examination of the urinary sediment for the leptospira, always remembering that this organism is not present in the urine till the twelfth day of the disease.

Seven-day fever.—A pyrexia remittent in type, with a tendency to relapse, together with a polymorphonuclear leucocytosis, should suggest the possibility of a fever being of spirochætal origin; the same is probably true of seven-day fever (p. 188), of which the saddle-back type of temperature chart constitutes the most striking feature.

Yellow fever.—The recognition of yellow fever in its endemic haunts calls for no special description, as it is made upon the general characters of the fever—the three-day incubation period, the icterus, the petechial hæmorrhages, black vomit, relative bradycardia, albuminuria, and usually a moderate polymorphonuclear increase. The hæmolysis may cause great difficulty in differentiating it from the bilious remittent form of subtertian malaria, which may simulate it very closely, especially where yellow fever occurs sporadically, as in West Africa, and where possibly the two diseases may coexist in the same case.

Dengue and phlebotomus fevers.—As regards the procedure in attempting a diagnosis in cases of pyrexia in which no parasites can be demonstrated, one can obtain a great deal of information, if not a probable diagnosis, from a differential together with a total leucocyte-count. A leucopenia with mononuclear increase and bradycardia is found in both dengue and phlebotomus fevers, and considerable difficulty may be experienced in differentiating these minor fevers from the graver ones already mentioned. Their respective endemic areas must be borne in mind; dengue, for instance, is common in the West Indies, the Pacific islands, and Australia, where sandfly fever is unknown or has not been recognized. Generally it occurs in a rapidly extending epidemic form. The joint- and bone-pains of dengue, the congested facies, the appearance

of the rash on or about the fifth day of the attack in a considerable proportion of cases, the conjunctivitis in phlebotomus fever—though this is sometimes difficult to recognize—must be taken into account. These fevers, when in epidemic form, tend to occur at different seasons; the former is a disease of summer and early autumn, the latter of spring and the closing months of the year—that is, at the times when their insect intermediaries most abound.

Undulant fever.—A continued pyrexia with the fastigium of temperature in the early afternoon, together with a comparatively clean tongue, rheumatic-like joint-pains, and profuse sweats, should suggest the advisability of applying the Widal test for *Brucella melitensis* or *paramelitensis*. But the clinician should not expect a positive result early in the course of the disease.

Enteric.—A pyrexia with the fastigium in the late afternoon towards six o'clock, with the clinical appearances of enteric and, it may be, a roseolar rash and relatively slow pulse, should suggest a fever belonging to this group, but a clinical diagnosis must be confirmed, whenever possible, in the laboratory. The serum diagnosis in *uninoculated persons* is not a matter of grave difficulty, though the reaction does not appear until the end of the first week; in the case of paratyphoid-A, however, it may not appear until considerably later, and this fact must not be lost sight of, and may explain many continued pyrexias of otherwise unexplained origin. A difficulty of considerable magnitude arises in *persons inoculated with a triple vaccine*. In these cases residual agglutinins to the respective organisms, typhoid, paratyphoid-A and paratyphoid-B, remain in the blood-stream for a year or more, and a serum diagnosis can only be made by employing frequent Widal tests and observing the rise in titre of agglutinins to one organism or the other (see Appendix, p. 868).

Further confirmation of the specific cause of an enteric-like fever may be obtained by isolation of the organism from the urine or fæces, but its late appearance in these excreta detracts from its value for early diagnosis. In cases where no laboratory confirmation can be obtained, Marris's atropine test may be employed.

Blood-culture still remains the most certain means of diagnosis in enterica and allied fevers, but a positive result can only be expected in about 30 per cent. of cases unless the blood is taken very early in the course of the disease. In confirming a diagnosis on clinical or serological grounds, the clinician should remember that the bacillus is usually absent from the blood-stream after the tenth day of the illness. (Chart 28.)

Typhus may be difficult to differentiate on clinical grounds from *relapsing fever*, and it should never be forgotten that the two diseases may coexist. In the absence of positive laboratory assistance, typhus may be mistaken for *smallpox*, either of the septicæmic or of the hæmorrhagic variety, early in the illness. In the differentiation, attention should be paid to the characteristic backache of the latter disease, and the appearance, on the third day, of the hæmorrhagic rash affecting the inner aspects of the thighs, the forehead, and the wrists in smallpox; while the bloated facies, suffused eyes, delirium, mental stupor, foul breath and coated tongue, with hyperpyrexia persisting beyond the third day without the appearance of a rash, should suggest typhus. The subcuticular or petechial rash of typhus (so difficult to recognize on a dark skin) appears

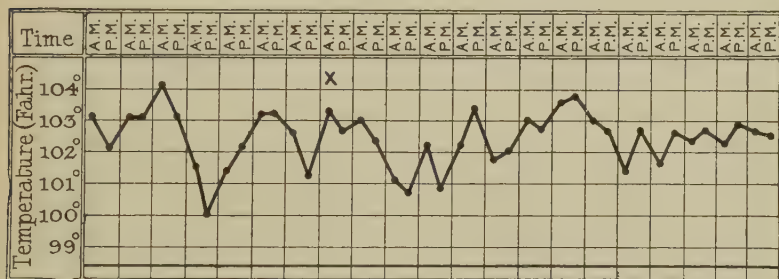


Chart 28.—Paratyphoid-B, four-hourly chart. (After Garrow.)

× Paratyphosus-B isolated from the blood.

on the fifth or sixth day on the inner aspects of the thighs, the umbilical region, and the inner aspects of the arms, spreading to the remainder of the body and rarely involving the face. The serum-reaction of this disease (or the Weil-Felix reaction) may be demonstrated after the fifth day of the illness. In *enteric*, hyperpyrexia and psychological changes rarely occur early in the disease; the differentiation from typhus on clinical grounds may be a difficulty, and immediate recourse should be had to blood-culture for *B. typhosus* (p. 866).

Liver abscess.—In the absence of any specific parasite in the blood, a minute study of a four-hourly temperature chart is a most necessary adjunct, especially in long-continued remittent fevers. A continued pyrexia in which the fastigium occurs towards evening, together with a polymorphonuclear leucocytosis of 9,000 or over, associated with a peculiar pallor of the face, profuse sweats, and, it may be, symptoms of involvement of the right lung, should make one suspicious of hepatic abscess, whether the

Entamoeba histolytica or its cysts are found in the fæces or not; generally a history of intestinal disturbance, not necessarily obvious, can be obtained. Rarely, hepatic abscess may occur without provoking any appreciable degree of pyrexia.

The **seasonal incidence of tropical pyrexias** may be of considerable assistance. Typhus, as a rule, is a disease of the cold or rainy season, when the native wraps himself up for the sake of warmth, and so encourages the propagation of the louse. For the same reason, *relapsing fever* is a disease of the early spring, to be followed at the commencement of the hot weather by *small-pox*. *Malaria* of *benign* and *quartan* varieties is a disease of the hot season, while the *subtertian* variety occurs most frequently towards the autumn months. The seasonal proclivities of *sandfly fever* and *dengue* have already been referred to.

Helminthic fevers.—An eosinophilia of 20–30 per cent. or over, with a leucocytosis, in a case of prolonged pyrexia should suggest a massive helminthic infection. When this blood condition is associated with intense muscular pains and intestinal symptoms, *trichinosis* may be considered, and may be confirmed by microscopic examination of an excised piece of muscle. On the other hand, an eosinophilia with a leucocytosis of 10,000–15,000 in a country where schistosomiasis (*Schistosoma hæmatobium*, *S. mansoni*, or *S. japonicum*) is endemic, in a patient with anæmia, emaciation, enlarged liver, tenderness over the gall-bladder, and a history of a blotchy urticaria, should lead to a thorough and repeated search of the urine and fæces for the characteristic eggs of these parasites. This urticarial fever is known in Japan as “katayama disease.” (Chart 29.)

Filarial fever.—An eosinophilia of 15–20 per cent., with a moderate leucocytosis, in an endemic focus of filariasis, whether associated with visible lymphangitis or not, assuming that no eggs of helminths are present in the stools, is strongly suggestive of filarial fever, even in the absence of the characteristic microfilariae in the blood.

Hyperpyrexia (104° F. or over), in a patient who is stuporose and is severely ill, suggests, at first sight, several alternatives. It may be a case of subtertian malaria, relapsing fever, pneumonia, smallpox, typhus, typhoid, heat-stroke, cerebro-spinal meningitis, or possibly plague. These are the alternatives that the tropical clinician has constantly to face. In the case of *subtertian malaria* and *relapsing fever*, positive assistance may be obtained from a microscopic blood-examination early in the pyrexia, and *B. pestis* may occasionally be demonstrated in a blood-film in *plague*

experienced in distinguishing the hæmorrhagic form from typhus in the early stages, but the smallpox tends to appear first on the pressure areas, thighs, sacrum, etc.

Scarlet fever, on the whole, is rare in most tropical countries and is for the most part mild. The generalized erythema, occurring after an incubation period of two days, its association with pharyngitis, the absence of severe joint-pains, a tendency to flaky desquamation, and a moderate leucocytosis assist in the diagnosis from *dengue*.

Measles has also to be taken into account ; the appearance of

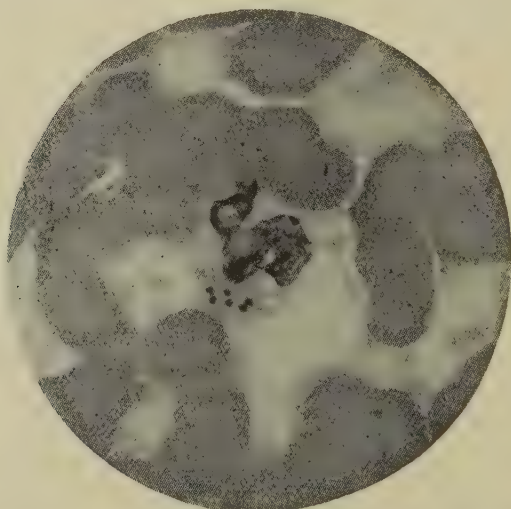


Fig. 62.—Pneumococci in leucocyte in peripheral blood.
(Orig. preparation. Microphoto : Dr. A. Norman.)

the rash on the fourth day of the disease, its predilection for the face, the associated nasal and conjunctival catarrh, the presence of Koplik's spots on the buccal mucosa, are points which serve to differentiate it from *typhus* and *dengue*. The roseolar rash of *rubella*, the mildness of the general symptoms, and the lymphatic glandular enlargement make the diagnosis sufficiently obvious, so that German measles in the tropics presents no essential difficulty. Finally, the multiform erythematous rashes sometimes encountered in *enteric infections*, especially *paratyphoid-A*, must be mentioned. Their resemblance to certain types of typhus rash is marked ; their appearance late in the fever, the absence of other clinical charac-

teristics of the former disease, and the assistance of laboratory methods must all be considered.

Japanese river fever and *spotted fever of the Rocky Mountains* are characterized by rashes which greatly resemble typhus and appear about the same period in the course of the disease (fourth to sixth day). The rash of the former commences on the face; that of the latter on the forearms and legs, and may subsequently involve the whole body. As factors in differential diagnosis they do not enter into account, except in those districts in which these two fevers are endemic.

Jaundice of hæmolytic origin is an important diagnostic feature in yellow fever, infectious jaundice, blackwater fever, the bilious remittent form of subtertian malaria, and relapsing fever. The icterus of *yellow fever* is sufficiently characteristic, is often associated with petechiæ, and does not occur until the third or fourth day. The icterus of *infectious jaundice* also occurs about this time, with pruritus, irregular pyrexia, and suffusion of the conjunctiva; it may be hardly recognizable, but there is usually a moderate splenomegaly. The intense jaundice of *blackwater fever* is dependent on the same cause, and appears simultaneously with the hæmoglobinæmia in severe cases. The yellow hue tends to deepen, and the diagnosis in this case is sufficiently obvious. The jaundice of *bilious remittent fever* (subtertian malaria) resembles that of yellow and blackwater fevers, but is generally of a lighter hue; it appears about the second day after the onset. The icterus associated with *relapsing fever* appears in severe cases during the pyrexial period immediately preceding the crisis, and is accompanied by great prostration and often by a painful enlargement of the spleen. In negroes suffering from lobar pneumonia, jaundice frequently develops about the third day.

Obstructive jaundice may occur late in the course of hepatic abscess, but is rare.

Glandular enlargement in association with tropical fevers is met with most commonly in bubonic plague, trypanosomiasis, filariasis, climatic bubo, rat-bite fever, and kala-azar. The adenitis of *plague*, *rat-bite fever*, and *filariasis* is a painful one. In the former two the path of entry of the virus can usually be ascertained. In *filarial* adenitis the existence of other glandular enlargement and the accompanying lymphangitis are of considerable assistance in forming a diagnosis. In *trypanosomiasis* glandular enlargement confined to the posterior triangle of the neck is uniform, generally painless, and discrete; gland-puncture will assist in diagnosis. In *kala-azar* the same group of glands may be involved, and on

excision the parasite may be demonstrated; mere puncture as a rule is unsuccessful. The glandular involvement of *climatic bubo* is generally subacute and unassociated with severe constitutional disturbance.

Diarrhœa is not usually a prominent symptom of tropical fevers. It may be noted, however, that a diarrhœa which may be hæmorrhagic is often associated with subtertian malaria, and may be present also in the enteric fevers and liver abscess.

Section II.—GENERAL DISEASES OF UNDETERMINED NATURE

CHAPTER XIX

BERIBERI, EPIDEMIC DROPSY, AND CENTRAL NEURITIS

I. BERIBERI

Synonyms.—Kakke ; Barbiers ; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and subtropical climates, and also, under certain conditions, in more temperate latitudes. The mortality is considerable, death usually depending on heart paresis.

History.—The special nature of beriberi was recognized by the Dutch in the early years of their intercourse with the East. Later, it was studied by British physicians in India, particularly by Malcomsen, Carter, Waring, and Morehead. It was not until a more recent epidemic in Brazil that beriberi began to receive attention from the present generation of medical men ; and only when Anderson, Simmons, Scheube and Baelz took up the subject in Japan was it studied by modern methods, accurately defined, and its true pathology apprehended. Scheube and Baelz were the first to show distinctly that beriberi is of the nature of a peripheral neuritis simulating that of diphtheria and of alcohol—a view subsequently confirmed and adopted by Pekelharing and Winkler, and by most subsequent observers. More recently, and mainly owing to the investigations of Eijkman, Braddon, Cooper, Fraser, Stanton, Funk, Vedder, Hopkins, Hausette, Chick, and Margaret Hume, its principal—it may not be the only—etiological factor has been shown to be a dietary of which the staple ingredient is overmilled rice or other cereal which has been deprived of a substance termed “ vitamin,” essential to nutrition.

Geographical distribution.—The area of the endemic distribution of beriberi is coextensive, probably, with the tropical and subtropical belts ; doubtless it still exists in many places where its presence is not generally expected. It was formerly the scourge of many of the mines and plantations of the Malay and Eastern Archipelago. It is apt to break out among the coolie gangs engaged on extensive engineering works in the tropics, such as the Panama Canal or the Congo Railway. It haunted the Dutch army in Sumatra, and

used to be common enough in the British armies in India. It is at home in many parts of Japan, particularly in her large, low-lying, damp, overcrowded cities. It occurs in China, the Philippines, the Eastern Peninsula, India, and Africa. We have had accounts of a small epidemic among a group of Western Australian natives, and also among Chinese on the eastern seaboard of Australia, a continent where beriberi was formerly supposed not to exist. Some years ago beriberi broke out in a lunatic asylum in Dublin; and apparently the same disease has been seen in similar institutions in the United States and in France, and also among the fishermen on the North American coast.

Epidemiology and endemiology. *Sex, age, occupation, etc.*—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called *infantile beriberi*, may declare itself in varying ways. The child may become aphonic, or extremely restless with incessant crying, or may exhibit signs of subacute meningitis, drowsiness, head retraction, and rotation of the eyes. It is rare in childhood and extreme old age, its favourite age being from about 15 to 30. It affects rich as well as poor. It is confined to no particular trade or occupation. If anything, it has a predilection for those who lead a sedentary life and are much indoors, as students, prisoners, and the inmates of hospitals and asylums. It is apt to attack pregnant or parturient females. It is quite as common in the strong and full-blooded as in the weak and anæmic.

Its seasonal prevalence varies in different regions, and is governed by economic factors, such as the yield of local rice crops and the consumption of milled rice.

Climatic conditions.—In countries with a hot and a cold season the epidemic outbreaks occur during the former, old cases improving and new cases ceasing to crop up during the winter.

Influence of overcrowding.—Overcrowding and unhygienic conditions generally seem to favour the outbreak of beriberi. This has, perhaps, a good deal to do with its frequency and virulence in Oriental jails, in schools, mining camps, plantation lines, armies, and ships.

Ship beriberi.—Beriberi is common in the native crews, more rarely, though occasionally, among the European officers and sailors, of ships on the high seas and far away from any recent telluric influence. The crowding in the damp fore-castle and the exposure incident to a sailor's life seem to be among the reasons, though not the only ones, for ship beriberi.

Since 1894 the disease has been common in the European crews of Swedish and Norwegian ships, which are in far better sanitary

condition than British ships, and yet beriberi is comparatively rare in the latter. The modern explanation of this occurrence is found in the fact that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet is inadequate in vitamin supply. Ship beriberi holds a place intermediate between true beriberi and scurvy, and is closely related to the disease found among the Rand miners of South Africa.

Asylum beriberi.—The Dublin lunatic asylum, built for 1,000 inmates, had 1,500 inmates crowded into it when beriberi broke out, so that the conditions resemble those found in a ship's fore-castle, already alluded to.

Etiology.—The earliest investigators of beriberi believed that it was a degenerative multiple neuritis indistinguishable from that produced by alcohol or diphtheria, and that it was due to an infection or intoxication, and much effort has been directed to the discovery of the poison. All these theories are now a matter of history, for they have been replaced by the food-deficiency theory, which it is now proposed to outline.

Food-deficiency theory.—This rests upon the conception that the neuritis is due not to the introduction of something foreign to the body, but to the deprivation of something essential to its healthy nutrition. Beriberi is thus a disease of deficiency, to use the expression of Funk.

However this may be, thanks to the pioneer work of Eijkman (1897), Braddon, Fraser, and Stanton, we now know that the beriberi of the Eastern Peninsula, of the Eastern Archipelago, of the Philippines, of China and Japan, is a sequel of a diet into which overmilled rice enters as the principal element, that is, rice from which the entire pericarp and germ have been removed; and that in this pericarp and germ there is a substance essential to the proper nutrition of the nervous system of man and of many other warm-blooded vertebrates.

If a fowl be fed exclusively on "*paddi*," that is, rice from which the husk has not been removed, the fowl will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time it will show signs of peripheral neuritis, lose weight, and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. If a fowl which, in consequence of such a diet, has begun to show signs of peripheral neuritis be given regularly some of the polishings of the rice, that

is, the dust or remains of the pericarp which had been removed in the process of milling, it will gradually lose the signs of neuritis, gain in weight, and recover. The neuritis—*polyneuritis gallinarum*, as it is called—is evidently the result of the deprivation of some element of food essential for the proper nutrition of the nervous system of the bird, and this element is located in the pericarp and germ of the rice grain (Figs. 63, 64). Almost miraculous recoveries

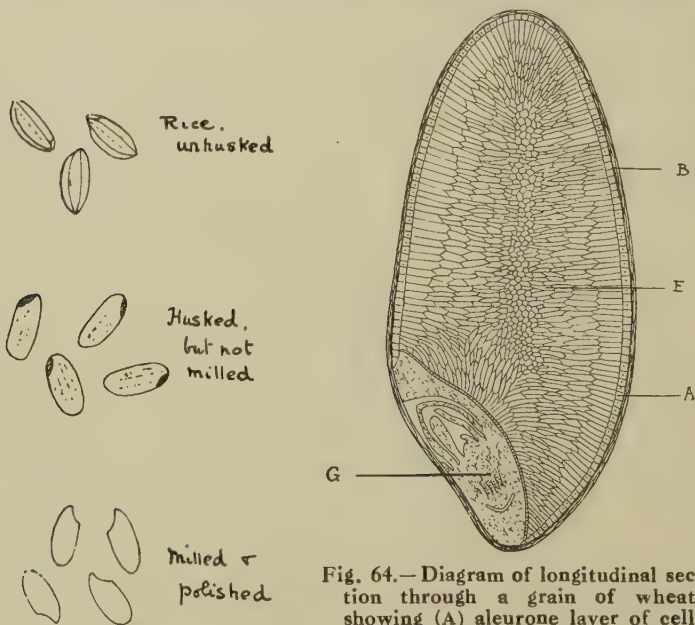


Fig. 63. — Showing the various stages in milling of the rice grain. (After Chick and Hume, "Trans. Soc. Trop. Med. and Hyg.")

Fig. 64. — Diagram of longitudinal section through a grain of wheat, showing (A) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (B) pericarp forming the branny envelope; (E) parenchymatous cells of the endosperm; (G) embryo or germ. (By permission of H.M. Stationery Office, from Dr. J. M. Hamill's "Report on the Nutritive Value of Bread made from Different Varieties of Wheat.")

in the stricken birds take place after hypodermic injection of an extract of the germ centre of wheat or other cereal.

The polyneuritis of the fowl is identical clinically and, possibly, etiologically with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result

is identical—beriberi is induced. Thus, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (a) the non-communicability of the disease, and (b) its production in man solely by means of diet. A similar condition has been produced in rats.

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130°C .—and that it is dialysable; that it is not a phytin or a fat, and that, although itself not containing phosphorus, the amount of phosphorus in any given rice is a reliable indication of the safety, or otherwise, of that rice as a staple article of food. Rice containing less than 0.4 per cent. of P_2O_5 they consider unsafe, and believe that its persistent use may lead to beriberi.

Acting on these findings, the governments of Singapore and the Federated Malay States interdicted the use of white or polished rice in their jails, lunatic asylums, schools, and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished from these institutions. Corresponding results have accrued from the same practice in Dutch Malaya, in the Philippines, and elsewhere. In India, however, as McCarrison has pointed out, the problem is not so simple. Decorticated rice is practically the staple diet of many millions in India, though beriberi is endemic only in a few circumscribed areas of Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India has to be considered as a fundamentally poor diet, whether of rice or other food grains.

True beriberi may therefore not be due to a complete absence of Vitamin B, but to an insufficiency of it.

It has been proved by Funk and others that a similar antineuritic body is present in other cereals and in a variety of food-stuffs. It seems probable that the destruction by heat in the process of canning, or otherwise, of this accessory factor, called by Funk "vitamin," the water-soluble B substance of McCollum and Davis—which exercises a curative as well as a protective action—may account for the prevalence of ship beriberi in Scandinavian ships, especially in long voyages during which such foods are an unavoidable necessity. In this respect there is a parallelism between beriberi and scurvy.

The period of development of beriberi in man has been determined by Fraser and Stanton as varying between eighty and ninety days.

Acton and Chopra have recently revived the idea that beriberi is due to ingestion of toxins formed usually in damaged rice, and occasionally also in dried fish and tinned provisions. These toxins are most readily formed in rice which has been deprived of its vitality by parboiling, and subsequently stripped of aleurone and other protective layers by overmilling, and which, when stored, is damaged by fungi and other bacteria. Some of these toxins, they conjecture, are water-soluble and affect the heart, others, alcohol-soluble, are neurotoxic.

Vitamins.—In a work such as this it is only possible to touch briefly upon this important subject; for further information the reader is referred to the Special Report of the Medical Research Council, No. 38, 2nd edit., 1924. Vitamins are widely distributed among foodstuffs. Though small in quantity, their influence upon metabolism is great; they are regarded rather as stimulants or catalysts than as entering into the structure of tissues, and are called accessory food factors. Their chemical nature cannot yet be stated with certainty. At least four of these substances are known, three of which are essential to nutrition. Fat-soluble A is the accessory food factor necessary to promote growth, and is intimately connected with the anti-rachitic vitamin D. Water-soluble B, or the anti-neuritic factor, is connected with the prevention of beriberi; xerophthalmia due to dysfunction of the lachrymal gland and hemeralopia (night blindness) are other consequences of a deficiency of this factor. Vitamins A and B are both comparatively stable, being destroyed by prolonged heating at a temperature of 100° C., while the latter, in the absence of oxidization, can withstand one of 120° C. for twelve hours. The third, vitamin C, which is present in fresh vegetables and fruits, is very sensitive to desiccation, is destroyed by prolonged heating at 100° C. in the presence of air, and is more commonly known as the anti-scorbutic factor.

Fat-soluble A is synthesized by plants, and is found in green leaves, where it is present probably in loose combination with some cell constituent. Treatment of ruptured leaves with alcohol and ether will remove the fat, together with the fat-soluble accessory substance. It is also present in cod liver, cod roe, various fish oils, green algae, diatoms, and in beef fat and butter; on the other hand, vegetables, seed oil, and to a lesser extent fruits and tubers, are deficient in the principle. Deprivation of this substance renders the organism liable to bacterial infection, especially of the intestinal tract. The amount present in milk varies with the diet of the animal. It has been suggested that vitamin A is closely related to cholesterol. Vitamin A is highly susceptible to oxidation, but is stable at high temperatures in the absence of oxygen.

Water-soluble B is contained in the cuticle of the grain and the outer or aleurone layer of endosperm, but the richest source is the germ or embryo of the cereal, which is also removed with the bran during the process of steam milling. Next to cereals come the pulses, even dried peas and beans, especially a Chinese bean, "kachang hijau," *Phaseolus radiatus*. Eggs and yeast are rich in this accessory factor; the latter is especially useful, as it can be extracted in a commercial preparation known as *marmite*.¹ Fresh meat, on the other hand, is comparatively deficient; the same may be said of butter and fat, fish, tinned meats, cheese, and vegetables. Miss Hume states that 1 gm. of marmite and 1.5 gm. of wheat-germ added daily

¹ Procurable from the Marmite Food Extract Co., Ltd., Mincing Lane House, 59, Eastcheap, E.C.

to a vitamin-free diet prevent ployneuritis. It is thought that the absence of vitamin B is responsible for what is known as war or nutritional oedema. In vitamin B deficiency also, atrophy of lymphoid tissue, thymus, spleen and Peyer's patches takes place.

Jansen and Donatti now claim to have isolated vitamin B in a pure state, in the form of a crystalline hydrochloride from rice polishings.

Vitamin C, the antiscorbutic factor, is produced in the germination of seed, and is contained mostly in fresh vegetables, green cabbage leaves, the juice of swedes, and the juices of citrous fruits, especially the lemon and orange, but the juice of fresh limes is inferior in this respect. Raw and tinned tomato juice contain a considerable amount of this substance, but the essential factor is absent both from vegetables and from fruit in the dried condition. Milk and meats contain very small quantities, but eggs, cereals, malt, preserved lime-juice, autolysed yeasts, pickles, none at all, or very little. The addition of acid or alkali to the water in which vegetables are boiled increases the loss of the antiscorbutic properties. In the absence of air the destruction of this vitamin is not so great.

Vitamin D is the antirachitic vitamin, which has some effect in promoting growth and is essential for the proper calcification of bones and the due formation of enamel in developing teeth. Vitamin D stands in a different position to the others, as it has been found possible to obtain it artificially by the irradiation of ergosterol with ultra-violet light. Vitamin D occurs in certain fats, notably cod-liver oil, in close association with vitamin A. It has been established that exposure to ultra-violet rays results in a mobilization of vitamin D in the body and hence has a curative action in rickets.

Vitamin E.—Recently a new vitamin has been described which is connected with the functions of reproduction. It is said to be contained in the fresh juices of vegetables, especially salad.

Predisposing factors.—Certain subsidiary factors predispose towards beriberi. Given the necessary food restrictions, any lowering of the general resistance of the body may lead to the rapid development of this disease. Thus, it often makes its appearance during pregnancy, lactation, after surgical operations, or during convalescence from infectious and debilitating diseases, such as dysentery, malaria, and enteric. Breast-fed babies of mothers suffering from the disease are themselves liable to suffer from it.

Pathology.—There is very little to be said about the post-mortem appearances in beriberi which is not covered by the accepted descriptions of the lesions of peripheral neuritis. There is a degeneration of the peripheral nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart, which may be the subject of an acute fatty degeneration like that in diphtheria. Degenerative nerve-changes may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus, with degenerative changes in its root in the floor of the fourth ventricle. Microscopically the nerve-trunks show changes from a slight medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Recent work on the nerve-changes shows that regenerative

processes occur side by side with the degenerative. (Fig. 65.) As a rule, some fibres in the vagus and sympathetic escape; thus the cardiac branches in the heart-muscle and the bronchial and oesophageal twigs are usually unaffected. The ganglionic cells in the spinal cord are only slightly affected. If there is anything peculiar about the post-mortem appearances in beriberi, it arises from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the



Fig. 65.—Longitudinal section of external popliteal nerve in beriberi.

One medullated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(Orig. case, from a preparation by Dr. A. C. Stevenson.)

right side, and great accumulation of blood in the right heart and in the veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less distinctive of beriberi as compared with other forms of multiple neuritis. The type of œdema indicates that it depends especially on vaso-motor disturbances, although cardiac weakness and partial

suppression of urine may be contributory elements. Œdema of the lungs also is not uncommon, and has, probably, a pathology similar to that of the connective-tissue œdema. There is no nephritis. The only lesion that might be considered specific in beriberi is the duodenitis, which may be present in acute cases during the first three weeks of the disease, though this is not invariable.

The general affection of the whole nervous system, involving the central and peripheral structures, is identical with that found in diphtheritic or alcoholic neuritis.

Symptoms.—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. As a rule, it is insidious in its onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without any development of symptoms referable to the nervous system. As a general rule, it is classified into two name-forms, according as the peripheral nerves or the cardio-vascular system are most affected. The former cases are known as paraplegic or “dry” beriberi, the latter as œdematous or “wet” beriberi. It must be understood that in all its forms beriberi is considered to be the same disease, and that a clinical classification has but a conventional value. In all clinical forms of the disease sudden death is liable to occur from heart-failure.

Paraplegic cases.—On examining one of the paraplegic cases referred to (Fig. 66), it will be found that, besides paraplegia of greater or lesser degree, there is a certain amount of anæsthesia or of numbness of the skin; particularly of the skin over the front of the tibiæ, the dorsa of the feet, the sides of the thighs, perhaps also of the finger-tips, and of one or two areas on the arms and the trunk. Deep sensibility elicited by compression of the Achilles tendon is usually numbed or entirely lost. The visitor may be struck with the thinness of the patient's calves and the flabby state of the gastrocnemii; and by the fact that if, whilst making the examination, he should handle these and the neighbouring muscles somewhat roughly, particularly if he should squeeze them against the underlying bones, the patient will call out in pain and try to drag the limb away. The thigh muscles may be similarly affected, and so may the thenar, the hypothenar, the plantar, and the arm muscles; like the calf muscles, these too may be wasted and flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat as well, the panniculus adiposus being everywhere meagre. If tested electrically, the muscles exhibit to perfection the reaction of degeneration. If the knee reflex be tested in the usual way, after the first week of the disease there will be no

response whatever : nor can any clonus be elicited. Occasionally a reflex contraction of the hamstrings may take place, giving a false impression of a knee-jerk. As a rule, all the deep reflexes are lost : but the superficial reflexes, unless in extreme conditions



Fig. 66—Ataxic or paraplegic beriberi, showing characteristic attitude. (*Orig.*)

of paresis and muscular atrophy, are usually present and more or less active. If, in severe cases, the patient is set to button his jacket or to pick up a pin, possibly he has a difficulty about it, or perhaps he cannot : he may bungle and fumble like an advanced ataxic. The fibres of affected muscles, when struck with a patellar

hammer, often contract locally in a particularly painful manner known as myœdema. There may be actual wrist-drop (Fig. 67).

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands ; and never or very rarely is there any paresis of the ocular



Fig. 67.—Paralytic beriberi, showing wasting of extensor muscles and wrist-drop. (*Orig.*)

muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. On the patient being got out of bed and started to walk, if he is able to progress at all his gait will be markedly ataxic ; but he is not ataxic merely, for, just as with the hands, it will be seen that, in addition to want of co-ordinating power, there is great muscular weakness. If he is laid on the bed and asked to raise his

legs, he is perhaps hardly able to get them off the mat, to cross them, or to place them one foot on top of the other. Very probably he is the subject of marked ankle-drop, so that he drags his toes when he

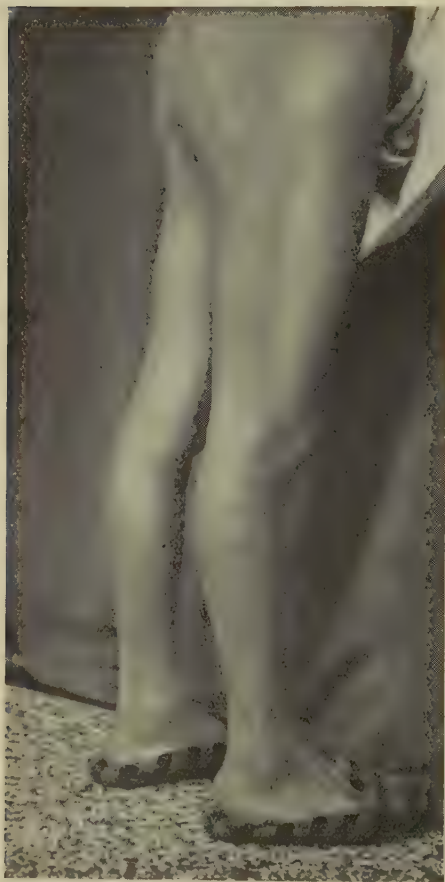


Fig. 68.—Recovery from paraplegic beriberi showing hyperextension of legs and posterior displacement of tibia due to laxity of ligaments. (*Orig.*)

attempts, in walking, to advance the foot; he has therefore to raise the foot very high, letting it fall on the ground with a flop when he brings it down again. His ataxia and his muscular weakness, as well as the partial anæsthesia from which he suffers, force him to adopt a variety of devices to assist him in progression. Manifestly, these patients are suffering from some form of peripheral neuritis. (Fig. 68.)

The general health is good for the most part; the tongue is clean, the bowels are fairly regular, there is no fever, and there is nothing amiss with the urine. Digestion, assimilation, and excretion go on satisfactorily.

The heart and circulation.—When the heart is examined, if the case be at all recent or moderately severe, attention is at once arrested. On inspection it may be remarked that the impulse is diffuse; that there

is epigastric pulsation; that the carotids throb too violently; that there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. On percussion the præcordial area is frequently found to be enlarged,

perhaps very greatly enlarged, especially to the right ; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second sound, is to be noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration ; so that the sounds of the heart are, like the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval like the beats of a badly-hung clock. It will also be observed that the



Fig. 69.—Wet or œdematous beriberi. (*Orig.*)

heart is very irritable, becoming easily quickened by exertion. It will be judged, therefore, that in addition to peripheral neuritis there is serious disease in the circulatory system, particularly in its innervation ; that there is dilatation of the right side of the heart ; and that there is a state of relaxed arterial tension.

Dropsical cases.—In the next bed, perhaps, to the patient whose picture has been drawn may be seen another suffering from apparently quite a different affection (Fig. 69). Instead of being wasted, his face is puffy and heavy ; his lips possibly are slightly cyanosed ; and his arms, hands, trunk, legs, and feet are distended with œdema. It may be thought from the œdema that it is a case of acute nephritis, but an examination of the scanty, dark-coloured urine shows that

it is of high specific gravity and contains no albumin, or only a mere trace ; so that the case cannot be one of acute Bright's disease. Careful observation will discover that the œdema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally cases are met with in which the œdema is peculiarly localized and fugitive. If attention be directed to the heart, a bruit and other evidences of dilatation of the organ and of arterial relaxation, just as in the first case, are discovered. Occasionally irregularity may be associated with slowing of the heart-beat, and it is probable that heart-block may occur in such cases. The pulse is invariably of low tension. If the lungs be examined, one may (or may not) discover signs of single or double hydrothorax, although, probably, not to a very great extent. The lungs themselves are healthy. On getting him out of bed it is found that the patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs, partly, perhaps, from some degree of paresis. He has ankle-drop, possibly ; and, if firm pressure be brought to bear on the calf-muscles through the œdema, signs of hyperæsthesia of the muscles may or may not be elicited. Knee-jerk is probably absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be complaint of præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—to a few ounces, even.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other case. In addition there is a somewhat firm œdema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected partly with lesion of the nerves regulating urinary excretion, and partly with the play of transudation and absorption in the connective tissues.

Great variety in degree and combination of symptoms.—Some cases are so trifling that the patients are up and moving about with more or less freedom ; other patients are so severely smitten that they lie like logs in their beds, unable to move a limb or perhaps even a finger. Some are atrophied to skeletons ; others are swollen out with dropsy ; and some show just sufficient dropsy to conceal the atrophy that the muscles have undergone. Though the cranial nerves above the seventh are very rarely involved, in some it will be noticed that the laryngeal muscles are paralysed, the patient being unable to speak above a whisper or to produce an explosive cough.

In one or two cases the abdominal and the perineal muscles may be so profoundly paralysed that, when the cough is attempted, at most a husky expiration is produced, while the belly is bulged forward and the perineum shot downward by the sudden contraction of the muscles of expiration. In practically all cases of over a fortnight's standing the knee-jerk and tendo-Achillis reflex are absent, though the latter often persists after the former has disappeared; at the very commencement of the disease these deep reflexes are exaggerated, gradually disappearing as symptoms develop, not to reappear for months, perhaps, after the patient is well in all other respects. In some epidemic outbreaks, as, for instance, in Mesopotamia in 1916, an irregular *pyrexia*, seldom exceeding 100° F., has been noted.

Uncertain course.—Beriberi slowly or rapidly declares itself after an incubation period as yet undetermined but variously stated as of weeks or months; it may be preceded by a period of intermitting languor, aching legs, palpitations, breathlessness, slowly advancing œdema of legs or face; or the patient may wake up some morning and find that during the night he has become dropsical or paretic. Thus the disease may develop slowly or rapidly. Equally uncertain are its progress and danger; within a day or a week, or at any time during its course, it may assume fulminating malignant characters. It may completely subside in a few days, or it may drag on for months. It may get well apparently and then relapse. It may, and generally does, clear up completely; or it may leave a dilated heart, or atrophied limb muscles with corresponding deformity. The variety in the severity, progress, and duration of beriberi is infinite; but in all cases the essential symptoms are the same—greater or less œdema, especially over the shins; muscular feebleness and hyperæsthesia, especially of the legs; numbness, especially of the front of the shins, of the finger-tips, occasionally of the lips; liability to palpitation from cardiac dilatation, and to sudden death from the same cause.

Cardiac attacks.—Most cases die from paresis and over-distension of the right heart, complicated and aggravated by œdema of the lungs or by diaphragmatic paralysis, by hydrothorax or by hydro-pericardium. Cardiac failure is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by œdema of the lungs. It can readily be understood how the establishment of any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

When we come to make a post-mortem in these cases we may find a heart slightly hypertrophied and enormously dilated, the right cavities distended with blood, the lungs and liver full of dark blood, and all the great veins engorged.

The nature of the underlying changes in the beriberi heart has hitherto been the source of speculation. Aalsmeer, in an electrocardiographic study of the heart in beriberi, finds that, even in the worst condition of failure, the beriberi heart gives a perfectly normal cardiogram, but the quickened rate of conduction of the cardiac impulse is accompanied by a consecutive shortening of the atrioventricular interval and that conduction decreases parallel with the progress of heart failure. These facts are very hard to reconcile with the well-known clinical observation of sudden right-heart failure in beriberi. The theory that the peculiar rhythm of the beri-beri heart is due to the degeneration of the vagus terminations in the heart-muscle can be rejected. The strange contrast between the evident weakening of the heart-muscle and the accelerated course of automatic contraction has given rise to the idea that the underlying cause might be water-retention and consequent swelling of the heart-muscle fibres; for the same phenomena are observed in experimentally-produced water-swelling of heart-muscle. This water-retention probably takes place in other muscular fibres in beriberi and its abolition is due to the absorption of vitamin B, so that the improvement of the condition of the heart and circulation in beriberi is accompanied by a marked increase in the urinary secretion (Wenckebach).

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 30 per cent. of those attacked; in others as low as 6 per cent., or even lower.

There are no grounds for attributing heart-failure to vagus paralysis, as is often done, for there is no clinical evidence that paralysis of the vagi is capable of producing this effect; the lesions of the cardiac muscle itself are most certainly responsible. This is the case in acute diphtheritic toxæmia, which resembles beriberi in the frequency with which sudden death ensues, while the degenerative changes in the cardiac fibres in beriberi greatly resemble those of diphtheria.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands, and in certain Pacific Islands, and causes a high infantile death-rate. It usually affects breast-fed infants of mothers who are either themselves victims of the disease or subsist on a diet poor in vitamins. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure. The majority of observers think that the maternal milk contains some highly toxic substance, but Vedder and his

American colleagues believe that the disease depends upon deficiency during uterine life and after birth of a substance in the milk which is essential to the growth and development of the child's nervous system. However, in children who die in this manner no imperfection or lack of development of the nervous system has been noted. In the most acute type it is children previously healthy, $1\frac{1}{2}$ to 3 months old, who are usually attacked; after a series of convulsive attacks the child suddenly dies of acute heart-failure. In less fulminating cases, vomiting, dyspnoea, dysphagia, and aphonia may precede the heart-failure. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting occur. In neither form has any true paralysis been noted, except that underlying the aphonia, which has been ascribed by Japanese workers to a paralysis of the left recurrent laryngeal nerve, from pressure by a dilated left auricle.

Some highly interesting suggestions have been made by G. W. Bray on the inhabitants of Nauru in the Pacific with regard to this question. The death-rate from infantile beriberi in that island amongst breast-fed babies from eight to ten weeks after birth, has been approximately 30 per cent. of the total deaths during the past twelve years. The mothers themselves show no signs of dietetic deficiency, though their dietary has been shown to be singularly deficient in vitamin B. Bray has been able to demonstrate the almost instantaneous effects of partially-fermented "toddy" (the sap of the coconut spathe), not only in the curing, but also in the prevention of this particularly fatal malady. The dosage of "toddy" is half-a-drachm twice daily during the first month, one drachm twice daily during the second, three times daily from three to six months, and over that age, three to four ounces weekly. In consequence of these simple measures the disease has ceased to exist amongst the Nauruans, while the incidence of a variety of other disorders, such as bronchitis, pneumonia, furunculosis and otitis media has to a great extent abated.

It appears that this peculiarly dramatic form of infantile beriberi has become prevalent since the use of "toddy" was prohibited by Government order. The therapeutic action of the toddy yeast in restoring these children is as rapid and dramatic as are similar extracts in artificially-produced polyneuritis of fowls and pigeons.

In the acute type of the disease gastroenteric, pneumonic, and meningitic signs and symptoms prevail. There is at first disinclination for food, followed by extreme restlessness, increased epigastric swellings, paroxysmal crying and general anasarca. Vomiting is the first sign of impending death. Dyspnoea and cyanosis supervene and the child dies in convulsions. (Fig. 70.) The temperature is slightly raised to about 100° F. A more chronic form of the disease is also recognized, as well as an insidious form in older artificially-fed children. The diagnosis of infantile beriberi is greatly aided by blood examination; a lymphopenia is almost invariably noticed with a total absence of small lymphocytes. Bray has been able to show that the therapeutic action of vitamin B is greatly enhanced by the synergic influence of vitamin A as in cod-liver oil.

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion, may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria, or of drugging with arsenic. The presence, actual or past, of oedema—especially of oedema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the *jongek* or “*squatting test*” is very useful. The patient, with his hands on top of his head, is unable to assume or rise from a squatting position. It must be

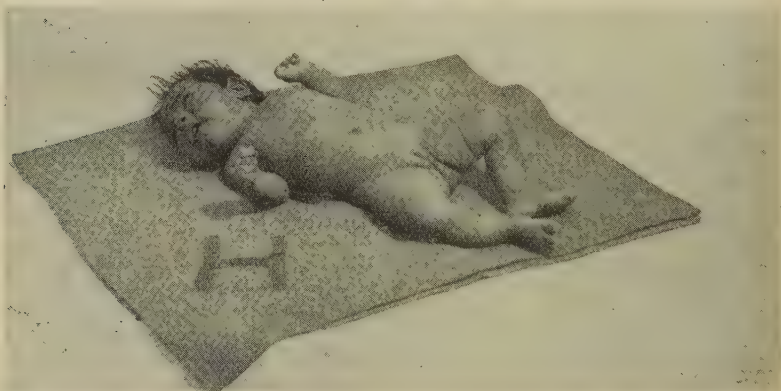


Fig. 70.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (Dr. G. W. Bray.)

borne in mind that slighter degrees of beriberic poisoning, evidenced only by slight anæsthesia of the prætibial skin area, by slight oedema of the same region, by slight hyperæsthesia of the calf muscles, and, perhaps, by impairment or absence of knee-jerk, may be the only symptoms present. True rheumatism is rare in the tropics.

Differential diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have over and over again been relegated to that refuge for ignorance, malaria, and called “malarial rheumatism,” or “malarial paralysis,” or, more pedantically, “malarial paraplegia” or “malarial neuritis,” though cases of subtertian malaria rarely simulate the clinical appearance of beriberi.

Beriberi can be differentiated from *alcoholic neuritis* by the tremors and mental disturbances which occur in this disease, and of which the diagnosis is generally obvious; from *arsenical neuritis* by the pigmentation, the diarrhoea, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from *chronic lead-poisoning* by the blue line upon the gums, the wasting of the muscles of the arms and legs which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from *lathyrism* by the presence of the knee-jerks and the absence of muscular hyperæsthesia in this affection. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

There are probably other forms of polyneuritis distinct from beriberi, but which may closely simulate the latter. Possibly these infectious forms of polyneuritis are occasioned by an organism as yet undetermined. Possibly also infective forms of polyneuritis occur in association with food-deficiency. These may account for sporadic cases in which pyrexia is prominent, and also for isolated outbreaks not associated with a faulty dietary.

McCarrison has noted that experimental pigeons in the pre-beriberi state—a state, that is, in which they do not exhibit any of the more alarming symptoms—are much more susceptible to extraneous infections; for instance, an infection of *B. suispestifer* may determine the onset of neuritis. It is not unreasonable to suppose that in man a microbic factor plays a similar part in the spread of some epidemics of polyneuritis which cannot otherwise be accounted for.

Prognosis.—The tendency to dilatation of the heart is the dangerous element in beriberi; it should be always before us and dominate our plans of treatment. It is wonderful how rapidly it may come on, and how quickly it may prove fatal. These sudden deaths, occurring sometimes from syncope—from instantaneous failure, as well as from the somewhat slower process of increasing over-distension—are constantly found in this disease. An absolutely favourable prognosis, therefore, ought never to be ventured on in even the mildest-looking case of beriberi, nor so long as the patient is exposed to the conditions causing the disease, nor so long as the neuritis appears to be active. That is a lesson which is often, and sometimes painfully, borne in upon the practitioner in beriberi districts.

Evidences of grave heart-implication, such as pulsating cervical vessels, equal spacing of the intervals between the sounds audible on auscultation, enlargement of cardiac dullness, especially to the right,

epigastric pulsation, a rapid feeble pulse, a distended stomach, cold extremities, cyanosis, dyspnoea, and a disproportion in the strength of the heart- and wrist-beats, are significant of danger. *Paralysis of the diaphragm, of the intercostal muscles, extensive serous effusions, very scanty urine*, are also unfavourable signs.

Vomiting.—No one can say when or how soon fatal implication of the pneumogastric and other cardiac nerves may take place, but vomiting is always an ugly and threatening symptom in beriberi; it probably indicates that the pneumogastric nerve is being attacked. The Japanese regard the occurrence of vomiting as of fatal import. Marked dilatation of the stomach has a similar significance.

Prognosis is improved if the patient is placed on a non-beriberic diet and is removed (that is before the heart-muscle or the cardiac or respiratory nerves are gravely degenerated) from the place in which the disease was contracted, to a healthy, non-beriberic, high-lying locality.

Treatment.—The first and most important thing to be attended to in the treatment of a case of beriberi is the diet. From this, rice, especially white rice, should be eliminated, and some article rich in vitamin—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal—substituted; and the patient should be removed, if practicable, to some place away from the endemic spot, to some dry locality, if such is available. He should sleep well off the ground in a thoroughly ventilated sunny room, situated in an upper story. He ought to clothe sufficiently and feed well, taking care that the food is of a varied and not of a bulky character, and that it contains a sufficiency of nitrogenous and fatty elements. Apart from other considerations, rice is a bad food for beriberics; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed even when they are dried; they are therefore indicated. Yeast has curative properties; the extract known as *marmite* may be given in doses of 1·5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed; but the mild cases had better spend the greater part of the day in the open air. If the disease break out on shipboard the dietary should be changed and the crew should be kept out of the fore-castle and, so far as possible, made to sleep on deck, properly protected from the weather by an awning.

With a view to diminishing to some extent the bulk of blood in

the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by means of full and repeated doses of some saline aperient. In cardiac cases small doses of digitalis or of strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1-per-cent. solution—of nitro-glycerin are indicated. The dose must be repeated every quarter- or half-hour, and kept up until the threatening symptoms pass away. In suddenly developed cardiac attacks, inhalations of nitrite of amyl, pending the operation of the nitro-glycerin, may be given. It is well for these two drugs to be in the hands of properly instructed ward attendants, so as to meet cardiac complication on its earliest appearance. There is often no time to send for the doctor. Should signs of cardiac distension and failure persist and increase in spite of these means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm, or, this failing for any reason, from the external jugular. Often, as the blood flows, rapid amelioration of the alarming condition sets in, and the patient is, for the time being, tided over an acute danger and given another chance. The bleeding should be repeated if the alarming symptoms recur, as they are almost sure to do. Oxygen inhalations, if available, are worth trying in cardiac attacks. Pleural and pericardial effusions should be sought for, and, if deemed to be interfering in the slightest degree with the circulation or respiration, drawn off with the aspirator.

Provided the patient is placed on a suitable diet and has been removed from the spot where he fell ill, and provided he can be tided over the first fortnight, he will probably recover; but, on the other hand, should he persist in a diet of white rice and remain in the place where his disease was acquired, though he may get over one or two cardiac attacks, he will almost surely die in some subsequent seizure.

In the case of breast-fed beriberic infants, they should be removed from the mother and handed over to a healthy wet-nurse, or placed on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, called "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 c.c. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. The use of toddy in infantile beriberi of the Pacific is referred to on p. 337.

For the atrophy of the muscles and anæsthesia of the skin, faradization and massage are of service, and should be employed as soon as the muscular hyperæsthesia has begun to subside. Strychnine, arsenic, and nitrate of silver are in repute as tonics in these circumstances. Hot-air baths are of considerable service. Care should be taken that permanent deformity does not occur from contraction of muscles. Foot-drop should be counteracted by Phelps's talipes splint with an elastic accumulator, and any other threatened deformity appropriately met. Relapses must not be risked by a return to the original diet or source of infection. The seaside or a sea-voyage has often a marvellously restorative effect.

Prophylaxis.—When beriberi breaks out in a school, jail, or similar institution, the place should be emptied of its inmates as soon as possible; at all events, those parts of the building in which the disease has appeared ought to be cleared out, and not reoccupied until they have been thoroughly cleansed, disinfected, ventilated, and dried. Overcrowding must be strictly avoided. Ventilation must be effective. The dietary should be revised and, if necessary, rice should be eliminated; it may be replaced by meat, flour, or beans. All the inmates should be obliged to pass the larger part of every day in the open air; their knee-jerks should be tested, and their legs examined for numbness, œdema, and muscular hyperæsthesia from time to time. Any suspicious case should be removed at once.

In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of white rice in countries in which rice is the staple food would not be politic, and could only lead to opposition and defeat the object in view; but the authorities, by educative methods and in other ways, can do much gradually to eradicate any prejudice there may be among the natives against undermilled rice. The committee on beriberi control of the Far Eastern Association of Tropical Medicine (1925) have urged upon governments that, wherever overmilled rice forms a staple diet, steps should be taken to discourage the use of rice from which essential food factors have been removed; that safe storage should be provided for undermilled rice; and that the use of accessory foods should be encouraged.

It is most important that a practical test for rice which may cause beriberi when used as a staple article of diet should be elaborated.

As a prophylactic, *marmite*, in small $\frac{1}{4}$ -oz. cubes, may be taken twice a week. Military and other expeditions should be warned

that tinned meats are notably deficient in antineuritic vitamins and require the addition of other foodstuffs to protect against beriberi as well as scurvy. Dried eggs are especially valuable, but are too expensive to be used on any extensive scale.

Contrary to what happens in scurvy, the human body does not appear to possess any appreciable reserve store of the antineuritic vitamin upon which to draw in a dietetic emergency. A constant supply, therefore, of the substance must always be maintained. The moral of this is, that for the prevention of beriberi for any population living on a restricted diet, such as soldiers and sailors on active service on land and sea, the germ and bran of wheat should be included in the manufacture of bread or biscuit where the rest of the ration consists of tinned or otherwise preserved foods.

II. EPIDEMIC DROPSY

Synonym.—Famine Dropsy.

Definition.—Epidemic dropsy is a disease closely related to beriberi. Clinically, it is characterized by dropsy associated with cardiac symptoms, but without marked paralysis or anæsthesia.

History and geographical distribution.—This disease was first noted in Calcutta, 1877–8; it has since occurred there sporadically, but vanishes in the hot season. In Mauritius, in 1879, it affected one-tenth of the coolies, of whom a large number died. An epidemic broke out in Fiji in 1926 and was curiously limited to Asiatics; no native Fijians were attacked.

Etiology.—Both sexes are attacked; children under puberty are less liable than adults; sucklings are seldom affected. The weak and the robust are equally susceptible. There are no direct observations on the germ of the disease, but there is indirect evidence of its portability and communicability.

Greig, who made a special study of the disease during the epidemics in Calcutta, concludes that in many ways epidemic dropsy resembles ship beriberi, while observations on war œdema seemed to indicate that a diet deficient in fats played the chief part; others, again, regarded the disease as due to a deficiency of calcium salts. Diminution of the circulating protein, by decreasing the osmotic pressure, may lead to œdema of the tissues, as Eckstein has demonstrated in the œdema of chronic parenchymatous nephritis. It is said that the disease is especially prevalent in Bengalis in India, and especially liable to appear as family outbreaks.

McLeod, after a careful analysis of all the evidence then available, concluded that epidemic dropsy was a disease *sui generis*.

But in epidemics of beriberi the absence of nerve symptoms is the exception—in fact, is very rare, and always concurrent with other cases in which nerve symptoms are pronounced, and with purely atrophic cases; such were not seen in the Calcutta or the Mauritius epidemics. Acton and Chopra regard epidemic dropsy and beriberi as different clinical aspects of a syndrome caused by ingestion of toxins formed usually in damaged rice.

The differentiation of epidemic dropsy from war œdema noted in Central Europe and Egypt during the Great War is difficult. The latter occurred in a population undergoing dietetic restrictions, and was characterized by great emaciation and a high degree of anæmia.

Pathology.—Beyond general œdema and occasional pleural and pericardial effusion, nothing special is remarked post mortem. There is said to be a diminution in the amount of albumin in the body, and a general wastage of all organs, including the endocrine glands.

Symptoms.—Dropsy is almost invariably present. It usually appears first in the legs, and in some instances is confined to the lower extremities; in others it spreads and involves the entire body. Occasionally it is very persistent, lasting and recurring during convalescence. Fever also is a very constant symptom; sometimes it precedes, sometimes it accompanies, sometimes it follows the dropsy. It is rarely high, ranging usually from 99° to 102° F. Diarrhœa and vomiting generally ushered in the disease in the Mauritius epidemic. In Calcutta these symptoms were not so frequent, although by no means rare there, occurring at both the earlier and later stages.

Nervous symptoms—such as burning, pricking, itching, and feelings of distension of the skin, sometimes limited to the soles and feet—often preceded the dropsy; and distressing aching of muscles, bones, and joints, worst at night, was usual. Anæsthesia of skin areas and paresis of muscles were never observed in Mauritius. The knee-jerk is not abolished. An exanthem, erythematous on the face, rubeolar on the trunk and limbs, was frequently seen in Mauritius, less frequently in Calcutta. It appeared about a week after the œdema, and lasted from ten to twelve days. Disturbances of the heart and circulation were prominent features in nearly all the cases. The pulse was weak, often rapid and irregular, the blood-pressure low; cardiac bruits were noted. Breathlessness on exertion occurred in all cases, severe orthopnœa in many. Signs of pleural and pericardial effusion, of œdema of the lungs, of pneumœnia, and of cardiac dilatation were common in Calcutta. Anæmia was usually present and marked; so were wasting and

prostration. The urine was not albuminous, but was of low specific gravity, and greatly increased in amount.

Treatment.—An analysis of the albumin-content of the blood will serve as an indication for the administration of albumin by the mouth. Egg- and milk-albumin are indicated in large quantities if such a deficiency is demonstrated. In other respects the treatment is symptomatic.

III. CENTRAL NEURITIS OF JAMAICA

Synonyms.—Peripheral Neuritis; Scott's Palsy.

Definition.—Under the term "central neuritis," H. H. Scott, in 1918, described a singular nervous disease tending to occur in epidemic form on sugar estates in Jamaica.

Etiology.—No definite information has so far been obtained regarding the true cause of this neuritis. The peculiar implication of the nervous system, associated with gastro-intestinal disturbance, and the analogy of beriberi and pellagra, certainly suggest a dietetic cause. The evidence points to some intoxication, and the fact that most of the cases occur on sugar estates during the months of May and June, when the dietary of those most affected consists almost exclusively of sugar, suggests some toxic element contained in or growing upon the fresh cane. In support of this view it is stated that cases cease to occur directly the crop is cut and disposed of.

Pathology.—The lesions in the central nervous system are marked and widespread; no portion appears to be specially involved. Scott found that most of the peripheral nerves had undergone Wallerian degeneration, while the posterior root ganglia and the spinal cord, especially the posterior zone, exhibited degenerative changes. The medulla, cerebellum, basal ganglia, and optic nerves were also affected. The analogy between this condition and the central neuritis of Adolf Meyer, and pellagra is suggested (*see* p. 353).

Symptoms.—In practically every instance the first symptom noted is a sensation of "itching in the eyes." The onset is sudden; in some cases both are attacked at the same time; in others only one eye is affected at first. The conjunctivæ are congested, and there is slight photophobia. At the same time the patient complains of a burning sensation in the mouth, with aphthæ of mucous membrane, and fissures at the angles; salivation is a common feature.

In a certain proportion of cases diarrhœa and intestinal symptoms are noted; the former may be so intense that the patient dies in a few days from exhaustion. In other cases constipation is the rule, and in these neuritic symptoms soon manifest themselves, partaking of the character usually associated with neuritis, such as a sensation of numbness and burning commencing in the feet and gradually extending up the leg; walking soon becomes impossible, and in the ataxia and retention of muscular power and of the deep reflexes the general resemblance to tabes is close, though the eyes react invariably to light. Sensation to pain, heat, and cold is usually retained in the limbs, and "girdle pains" occur in a certain proportion of cases.

Recovery is the rule in milder cases, though certain residual symptoms, such as indistinctness of vision, deafness, and a peculiar "steppage gait" with foot-drop, may result. The sphincters are never affected till the end.

Treatment.—This appears to be dietetic and symptomatic only.

CHAPTER XX

PELLAGRA

Synonyms.—Mal de la Rosa ; Mal Rosso ; Alpine Scurvy ; Asturian Rose ; Psilosis Pigmentosa.

Definition and description.—An endemic disease of slow evolution, characterized by a complexity of nervous, alimentary, and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn months), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are—(a) a remitting dermatitis of the exposed parts of the body ; (b) marked emaciation ; (c) profound depression alternating with mania.

History.—The history of pellagra is comparatively recent. In Spain it was first described by Casal in 1762, under the name of *mal de la rosa*. In Italy the disease, under the name of Alpine scurvy, was described by Odoardi in 1776. The earliest mention of pellagra in France dates from 1829. We know nothing of the history of pellagra in Egypt prior to the publication of Pruner's "Topographie Médicale du Caire," in 1847. In the United States of America, although there is evidence of its sporadic occurrence there for a considerable time—at least fifty years—before its nature was recognized, pellagra was first diagnosed as such in 1907. It is especially prevalent in the south-eastern States. Dr. H. F. Harris, Health Officer of the Georgia State Board of Health, estimated that there were 50,000 cases of pellagra in his State, and in 1916 it was estimated that there were 150,000 pellagrins in the southern United States alone.

Since 1912 sporadic cases of the disease have been reported in the British Isles.

Geographical distribution.—*Europe*: Pellagra is found in northern Portugal, in Spain, in Italy, in the south-west of France, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Serbia, Bulgaria, Turkey, Greece, Corfu, Rumania, Bessarabia, Kherson, Poland. Sambon has shown that, though hitherto practically unrecognized, it prevails endemically throughout the British Isles. A few cases have been reported from Germany. *Africa*: Algeria, Tunis, Egypt, the Red Sea coast, Rhodesia,

Nyasaland, and among the Kaffirs and Zulus. *Asia*: It has been reported from Asia Minor and North Behar in India, the Malay States, the Philippine Islands, Japan, China and Korea. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the Great War. *America*: the United States, Mexico, Central America, Brazil, the Argentine, Barbadoes, Jamaica, and probably in other West India Islands. *Australasia*: Pellagra has been reported from New Caledonia.

Epidemiology and endemiology.—An important epidemiological feature of pellagra, in addition to those already mentioned, is the marked fluctuation of its prevalence from year to year. Thus there may be long periods of quiescence, followed by years of considerable activity during which the disease may be looked upon as a new invasion. Pellagra is not contagious. The sound may associate with the sick and remain healthy. Doctors, nurses, and attendants on pellagrins are not known to contract the disease. Pellagrous wet-nurses do not infect their charges, and attempts to transmit the disease by inoculation have failed.

Associated diseases such as ancylostomiasis, schistosomiasis, tuberculosis, sprue, dysentery, and syphilis play a very important part in favouring the development of pellagra, in accelerating its course, in modifying and aggravating its symptoms, and in determining its mode of termination.

Season.—Of all diseases with marked seasonal connexion, pellagra is one of the most striking in this respect. As in the case of malaria, the pellagra season varies in different localities, but is always the same in the same locality.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreak being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seems to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a less extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met with at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might lead one to believe that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect part in the etiology.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Hitherto, pellagra was considered to be a disease of middle age, the majority of cases occurring between 20 and 50. Sambon has shown that within the endemic centres children are attacked, and that no age is exempt, he having seen the characteristic symptoms in a woman over 100 years old and in infants of barely 3 months.

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, enjoy an immunity similar to that of town-inhabitants as regards malaria. Felix points out that pellagra is quite exceptional among the Jews, who, as a race, rarely engage in agriculture.

Etiology.—Pellagra has been ascribed to the most varied causes, such as insolation, poverty, insanitary dwellings, syphilis, irritant oils, bad weather, alcohol, garlic, onions, maize. Some have regarded it as “sunstroke of the skin.” “Sun disease” was an old popular name, and certainly the skin manifestations of pellagra are influenced by the action of the direct rays of the sun. This was proved experimentally, first by Gherardini, who varied the limits of the eruption by systematically displacing parts of the clothing; and later by Hameau, who obtained differently shaped patches of erythema by means of gloves fenestrated in different ways. In smallpox, and also in other exanthemata, we notice a decided influence of light, more particularly of the actinic rays, on the production of their skin eruptions. Although light may influence the eruption in pellagra, this is no adequate reason for concluding that insolation is the cause of the disease, any more than that it is the cause of smallpox. In support of the sunlight hypothesis, certain experiments on the effect of sunlight on animals fed on a too restricted (unphysiological) diet have recently been advanced; but it is evident that this cannot be the whole, though it may be part of the truth.

Three main theories have been advanced for the causation of pellagra, and the evidence in favour of each of them must be categorically stated. These theories may be termed (1) the intoxication theory, (2) the infection theory, (3) the food-deficiency theory.

1. *The intoxication theory.*—The general opinion is that pellagra appeared soon after the introduction of maize into Europe, and that it advanced *pari passu* with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize is still held by many to be the causative agent of pellagra, just as a certain condition of rye is known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Lombroso and Bellardini, in 1871, first advanced the theory that the prevalence of pellagra in Italy was due to the consumption of diseased maize, and their ideas subsequently formed the basis for public measures against the disease in that country, as well as in Southern Europe. A large amount of work has been done upon the saprophytes which attack the grain. Maize may be damaged through damp or through being insufficiently cured, and in that state acts as a medium for the growth of poisonous fungi of different varieties, such as yeasts and moulds—*Penicillium glaucum*, *Mucor racemosus*, *Aspergillus niger*, and *A. fumigatus*. Lombroso claimed to have produced pellagrous symptoms in fowls by injection of alcoholic and watery extracts of damaged grain, but subsequent experiments made on the same lines can in nowise be considered confirmatory.

While it is certainly true that pellagra occurs commonly in those countries in which maize flour enters largely into the composition of bread, in this manner forming the staple article of diet, yet it is difficult on this basis to account satisfactorily for the sporadic cases of this disease which have been reported from the British Isles, Germany, Poland, and China, where maize does not enter the dietary.

That pellagra is due to poisons elaborated from maize *within the alimentary canal* (another hypothesis), is disposed of by the harmlessness of this cereal in non-pellagrous districts.

Shelley in Nyasaland thinks that pellagra is due to absorption of a toxin which produces a neuritis of certain peripheral nerves, since the skin lesions are most marked in the areas supplied by the lower cervical, the lower lumbar and first sacral nerve roots.

2. *The infection theory.*—Sambon since 1905 has been the staunch antagonist of the maize or “*zeist*” theory. On epidemiological grounds he has maintained that pellagra is a protozoal disease, and points to *Simulium* or *Culicoides* midges as being the probable transmitters of the hypothetical parasite. It cannot be said that this hypothesis has received much support.

Jobling, Arnold, and Babes have attempted to prove that the sensitization of the skin and other symptoms of pellagra may be due to a photodynamic intoxication; they have found in the *fæces* fungi capable of producing photodynamic substances. The ultimate result of their technique was to produce fluorescent cultures, which were inoculated into mice, when it was found that these animals died on exposure to sunlight.

No satisfactory evidence has yet been adduced that pellagra can in any sense be considered a directly infectious disease. Goldberger's carefully conducted experiments in 1917 would seem to dispose of this view entirely.

Goldberger obtained sixteen volunteers who, under his direction, attempted to infect themselves by ingesting skin scales, naso-pharyngeal secretions, and epidermal excretions, over a period of six months. During this trying period they were, and subsequently remained, quite healthy.

3. *The food-deficiency theory.*—Deeks in 1912, and Funk in the following year, suggested that pellagra is a disease produced by a deficiency in diet. Many observers now believe that pellagra, together with beriberi and scurvy, belongs to the “food-deficiency” diseases and is due to lack of certain vitamins in the food. The experiments conducted by Goldberger and Wheeler in America are the most telling so far published in favour of such a hypothesis.

In 1914 they fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six of the number developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in banishing pellagra from an orphanage asylum in which up to that time the disease had been in evidence.

There are those who think that preserved and tinned food may conduce to pellagra, owing to destruction of the vitamins in the process of conservation. A certain amount of evidence in favour of this view has been obtained in the southern United States.

The results of the Commission which investigated the prevalence of pellagra among the Turkish prisoners in Egypt tended to show that the error of metabolism in the disease is manifested in a primary deficiency of “biological proteins.” A large number of cases occurred among the Turks, and later among the Germans. In the former, out of 105,468 prisoners, 9,257 cases were recorded, while there were 79 German cases out of 7,600 prisoners. During the year 1919, 1,617 deaths occurred among the Turks from this cause, and 6 among the Germans. Wilson and Roaf, members of the Commission, suggested that in a susceptible subject, whose protein assimilation is sufficient for all needs while at rest, pellagra may develop when bodily needs are increased by physical labour, or when his faculty of metabolism has been vitiated by damage to the powers of alimentary absorption, as, for instance, by bacillary dysentery or other intestinal disease; in these cases a considerable loss of protein-absorption power was noted, the power being reduced to less than 67 per cent. It was noted further that, as long as the prisoners were at rest, pellagra was in abeyance, but broke out immediately they were subjected to any exertion. It would appear from these observations that, in an individual whose balance of protein metabolism has been undermined for a sufficiently long period, subsequent feeding with a suitable dietary may not prevent the appearance of pellagrous symptoms.

The assessment of the biological value of proteins in various

articles of diet has brought out the interesting fact that maize is particularly deficient in this respect. Thus recent developments in the study of pellagra are tending to bring the food-deficiency theory and the original "maize theory" of Lombroso into line.

The protein of maize flour, *zein*, is deficient in certain amino-acids, tryptophane and lysine, essential constituents of all proteins of proved biological value and known to be essential for nutrition. Millet and many other cereals contain a greater proportion of protein of biological value; and, if this be the case, a plausible explanation is obtained of the rarity of pellagra in Upper Egypt and the Sudan, where millet forms the staple article of diet, and the prevalence of the disease in the Delta, where maize is largely consumed.

A protein deficiency need not be peculiar to a maize dietary, and in this manner it is possible to account for the sporadic distribution of pellagra in countries in which maize is not consumed.

Biological protein value (B.P.V.).—The amount of gross protein in a diet affords an unsatisfactory basis of comparison, in that the vegetable protein is much less suitable for assimilation than that derived from animal sources. It has been found that only certain amino-acids contain nitrogen in a form which can be utilized for rebuilding tissues. From a consideration of these facts the expression "biological value of protein" has been derived. The smallest amount of meat protecting a man of 70 kilos from a loss of body protein is 30 grm. per diem, of bread 76 grm., and of maize 102 grm. Wilson has suggested, as minimal amounts per diem, a biological protein value of 45 grm. (a figure representing a gross protein value of 120 grm. per diem) for heavy labour and 40 grm. for light labour. A diet containing 80 grm. per diem gross protein value and less than 33 grm. biological protein value would seem to predispose towards the development of pellagra, as in the case of the Turkish prisoners already referred to; in these the diet responsible for a large number of cases had a B.P.V. of 33·5 for non-labour and 36·8 for the labour groups.

Deficiency of protein may take one of four forms:

1. Absolute deficiency of intake below the normal requirements.
2. Deficiency relative to individual requirements.
3. Deficiency due to low availability of protein resulting from the nature of the food or defective methods of preparation.
4. Secondary deficiency due to excessive bacterial destruction of protein in the intestine or defective powers of digestion or assimilation.

The following is a table, compiled by the Medical Research Committee, of the "biological values" of various proteins, as measured by the relative "tissue-repairing" values of equal weights:—

Ox-meat	104	Caseinogen	70
Cow's milk	100	Peas	56
Fish	95	Wheat flour	40
Rice	88	Maize meal	30
Potato	79		

Attempts have been made to produce pellagra in monkeys by feeding them on a low protein dietary. Chick and Hume have reported successes in three cases in which the animals were permitted such accessory food as butter, marmite, and orange-juice, while the main diet consisted of sugar, cornflour, salt, and corn gluten, the latter forming the only source of protein. A high degree of emaciation and hyperæmia of the hands and face when exposed to strong light was produced in monkeys in this manner. It is difficult, however, to be certain that the state produced is analogous to pellagra in man. As in beriberi, so in pellagra, it is not easy to fit in all the facts of the case with one theory, however plausible. An illustrative instance has come under the Editor's personal observation; it is thus reported by Enright: In January, 1919, a number of German prisoners in Egypt, who up to that date had remained healthy, developed symptoms of pellagra, although, according to their own statements, they had always received an ample protein dietary, both before their capture in Syria and during their four months of captivity in Egypt; while no extensive outbreak of pellagra among the half-starved masses of Central Europe consequent upon the Great War has been recorded.

Watson, mainly on pathological grounds, believes that an intimate association between central neuritis and pellagra exists. In both conditions a certain set of neurones is liable to be involved, and the cause of this affection in both may be an endogenous toxin acting through the agency of the endocrine system upon unstable neurones.

In this and other ways the rather confused state of our knowledge on the intoxication and food-deficiency theories may be harmonized. Skin sensitization, such as occurs in man in pellagra by the rays of the sun, may be brought about in animals, especially sheep, by feeding them on different forms of clover, trefoil and lucerne. This is thought to be due, not so much to the lack of certain essential nutritive principles, as to the absorption of toxins which have a selective action on the central nervous system over a sufficiently long period.

Misses Chick and Roscoe now think that pellagra may be caused by a lack of vitamin B, which contains two factors—a thermostabile pellagra-preventing factor and a thermolabile antineuritic

factor. Young rats deprived of vitamin B develop a skin condition resembling pellagra.

Pathology.—The pathological features essential to pellagra are usually obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting of their muscular coat, while at the same time the mucous lining is hyperæmic and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish in colour, but may be the seat of hæmorrhages.

There may be actual wasting of the brain, the ventricles being distended by an excess of fluid. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually escape. The anterior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion being often degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change; there is usually no increase in the globulins.

Mott remarked, as to the changes in the cerebrum, cerebellum, pons, medulla, and spinal cord, that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxæmia, possibly in the manner already suggested above. The posterior spinal ganglia cells show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a less degree. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or subacute combined degeneration of the cord.

Symptoms.—The course of pellagra is generally long. The disease does not pursue any regular course, but one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances. It is possible that these may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar staring look, and complains of headache, giddiness, and vague but often severe pains in the back and joints. His character changes; he becomes irritable, and at the same time stupid and morose.

At times the tongue is coated; later it loses its epithelium, the denudation extending not infrequently to the palate and gullet,

and giving rise to a sore condition, often accompanied by a saltish taste and copious salivation. Associated with this is a leucoplakia at the angles of the mouth. The gums may be swollen and bleed easily, a condition which gave rise to the name "Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower part of the abdomen are tense and painful. Constipation may be present, but in many instances there is diarrhoea of pale fermenting stools resembling those of sprue.

The skin symptoms.—Most observers regard the skin lesions of pellagra as the earliest manifestation of the disease, but possibly they are symptomatic of some chronic and grave constitutional disturbance. At first an erythema, not unlike a severe sunburn, is observable on parts of the body which are, as a rule, unclothed and exposed to the sun. (Plates XVI, XVII.) The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on the female genitalia. The patches of erythema are irregular in outline and intensity. Very characteristic are the symmetrical patches behind the mastoid processes, a ring or collar round the neck, and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The character of the eruption is well shown in the Plates. In the case shown in Plate XVII it was limited on the feet by the outline of the Turkish slippers the patient wore. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts, and blebs with clear, opaque, or blood-stained contents of feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by desquamation, which leaves the skin rough, thickened, and permanently stained of a light sepia colour. This is especially marked on the back of the hands and on the elbows, and forms recognizable evidences of the disease. It is on account of this roughness of the affected skin that the disease is called "pellagra," an Italian word meaning rough skin. An obstruction to the sebaceous ducts on the *alæ nasi* produces a peculiar sulphur-flaked appearance of the skin in that region.

Implication of the *nervous system* is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. Coarse tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the dis-



1



2



3

Fig. 1.—Characteristic inflamed tongue of acute pellagra.

Fig. 2.—Early pellagrous rash, with cellular infiltration and pigmentation.

Fig. 3.—Typical pellagrous rash over occiput and mastoid processes, with formation of "rosary" round neck.

PELLAGRA.



ease progresses. Muscular cramps may occur, and a definite ankle-clonus is often seen. The patient suffers from obstinate sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Another characteristic symptom is a feeling of burning in the palms of the hands and the soles of the feet. Chvostek's sign, mechanical irritability of the facial nerves, is said to be present in the majority of cases.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwoman's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule there is no marked permanent elevation of temperature, but periods of slight fever occur at irregular intervals.

Two or three months after onset the symptoms abate and, although the affected skin areas remain dark-coloured and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases; the patient loses weight and is unable to work; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhœa may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhœa, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years; it usually extends to ten, fifteen, or more.

In a proportion of cases, more especially if the patient leaves the endemic area and comes under favourable hygienic influences early in the disease, recovery may take place.

Cases differ considerably. In some the nervous symptoms predominate, in others the gastro-intestinal, in others again the cutaneous. Forms of hyperæsthesia may occur in different regions

of the body. Ocular symptoms, such as ptosis, diplopia, amblyopia, mydriasis, are not uncommon. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts and traces of albumin and, usually, indican. The erythrocytes and hæmoglobin are diminished to a limited extent in the uncomplicated disease. As a rule there is a definite lymphocytosis, but it cannot be said that, although usually disturbed, the differential leucocyte-count is constant or characteristic. The gastric juice is deficient in hydrochloric acid.

A very acute form has been described under the name of "pellagra typhus." In this there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions. In extensive outbreaks of pellagra, such as occurred among the Turks during the Great War, cases of this description may be comparatively common.

It has been estimated that in Italy from 4 to 10 per cent. of the pellagrins become permanently insane. Similarly, in the United States of America the pellagrins are becoming numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane.

Epileptiform convulsions may rarely occur. The time of the appearance of mental symptoms is subject to the widest variation. They may be seen as primary symptoms, or may occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and the occurrence of katatonia. As a rule, restlessness, vertigo, and insomnia anticipate the characteristic melancholia.

Diagnosis.—Of course, doubtful cases are occasionally encountered, but a localized erythema associated with nervous symptoms, particularly mental symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for acrodynia, erythema, eczema solare, trade dermatitis, lupus erythematosus, or syphilis; the gastro-intestinal disturbance and the glossitis for sprue; while the nervous manifestations have to be differentiated from hysteria, general paralysis of the insane, ergotism, and lathyrism.

Treatment.—Arsenic in large doses is now regarded as a drug of value in the treatment of pellagra. Fowler's solution by mouth—5 drops two or three times daily, increased by 1 drop daily until evidences of a toxic nature are induced—or hypodermically in combination with bicarbonate of soda (3 to 5 gr.) two or three times a



Photo: Dr. A. D. England.

PELLAGRA RASH ON FEET.

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes.

week, is said to be productive of good results if given early in the disease, and, of course, combined with good hygienic conditions and removal from the endemic area. Atoxyl, soamin, and salvarsan have also been commended. No case should be regarded as cured until the patient has been absolutely free from all symptoms for at least two years.

In early stages remarkable improvement is noted with a dietary rich in protein, such as meat and eggs, although in the advanced stages this is useless, and the disease may then be regarded as incurable. In Italy the Government, basing its action on the maize theory of pellagra, has provided grain-drying appliances for bakeries, and other hygienic advantages, including better house accommodation, also special asylums (*pellagrosari*) for the treatment of the disease in its earlier stages. It is stated that a decrease of the malady has followed these measures. Nevertheless, pellagra seems to have increased of late years, especially around Perugia and in other districts of Northern Italy in which these measures have been most strictly carried out.

Goldberger strongly advocates the employment of dried yeast in doses of 15 to 30 grm. daily in table syrup, in addition to dietetic measures in the treatment of pellagra. On the assumption that the skin lesions of pellagra are in some way connected with changes in the thyroid gland, Shelly has advocated thyroid extract in 1-gr.-doses daily.

Prophylaxis.—In view of the uncertainty regarding the true etiology of pellagra, prophylactic measures should at present be based upon sanitary surroundings and the administration of a well-balanced diet containing an abundance of animal proteins and vegetables.

CHAPTER XXI

SCURVY IN THE TROPICS

EPIDEMICS of this disease are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary; this is especially the case in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of consuming large quantities of fresh vegetables and fruit such as bananas.

Etiology.—Scurvy is now generally regarded as a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin. This body (p. 326) is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but reappears directly these latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved *lime*-juice little or none at all, while preserved lemon-juice is rich in this substance.

The antiscorbutic factor is soluble in water and in alcohol, and will pass through dialysing parchment, or a porcelain filter, without appreciable loss. It is more stable in acid than in alkaline media.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses the gums present fungating masses projecting beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing *around the hair-follicles*, especially on the thigh. Hæmorrhages occur into the muscles of the thigh and into the knee-joint. Very painful effusions under the periosteum form irregular nodes, which may break down and

ulcerate. Œdema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The urine is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more constant than diarrhœa. The psychical disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy occurs endemically in the mine-workers on the Rand. Darling and others have noted that a certain proportion of these cases are distinct in a clinical sense from those seen elsewhere. In this variety, known as *Rand scurvy*, the spongy gums and loose teeth that occur in the classical type of the disease may be absent, while the heart undergoes primary hypertrophy, with subsequent dilatation suggestive of beriberi, though the neuritic symptoms of beriberi are absent, and the knee-jerks are actually exaggerated. Rand scurvy tends to occur especially among gangs of native labourers when fed upon an unsuitable dietary; this is particularly the case in natives from the Congo and tropical Africa, who have been in the habit of consuming large quantities of fresh vegetables and fruits, and who when at work in the mines are fed upon dried cereals and preserved foods. The number of these cases is very large indeed. Donaldson reports that in 1920 more than 200 cases of scurvy were treated in one hospital, of which number one-third occurred within three months of entering the mines. It has been found that scurvy in these natives predisposes to all kinds of bacterial infections, and especially to pneumonia.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter. But care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosing scurvy in the early stages, especially in children, has been devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated till the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy.

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocurable, fresh meat can be substituted, but is by no means so satisfactory. Germinating peas are useful when fresh vegetables are unobtainable. The following method of using peas and other pulses is recommended by Chick and Hume:

SUGGESTED METHODS OF PREPARING PEAS, LENTILS, OR OTHER PULSES FOR THE PREVENTION OF SCURVY, IN THE ABSENCE OF FRESH VEGETABLES

1. The dry seeds must be whole, retaining the original seed-coat, and not milled or decorticated.

2. They must be soaked in water for several hours; the time necessary depends on the temperature—24 hours at 50° to 60° F., and 12 hours or less at 90° F.

3. The water must then be drained away and the peas, etc., allowed to remain in the moist condition with access of air. They will then germinate and the small rootlet grow out. . . . This germination will take 48 hours at 50° to 60° F., and 12 to 24 hours at 80° F.

Soaking.—The peas or other pulses, placed in a *clean* sack, should be steeped in a trough, barrel, or other suitable vessel, full of clean water, and should be occasionally stirred. The sack and trough, etc., should be large enough to allow for the swelling of the peas to about three times their original size. In a hot climate 6 to 12 hours should suffice for this soaking.

Germination.—The peas should be lifted out of the water and spread out to a *depth not exceeding 2 to 3 inches* in a trough or other vessel with sides and bottom porous or well perforated with holes; this is to allow *complete* access of air. *The seeds must be kept in a moist atmosphere*, by covering with damp cloth or sacking, which is sprinkled (by hand or automatically) as often as is required to keep the peas thoroughly moist underneath. . . . *All the vessels should be clean.*

4. *It is important that the germinated pulses should be cooked and eaten as soon as possible after germination, and should not be allowed to become dry again; in that case the antiscorbutic properties acquired during the process of germination will again be destroyed. The pulses should not be cooked longer than necessary (see p. 327).*

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a very definite curative value. Canned vegetables, with the exception of canned tomatoes, are useless.

In the case of natives, the most valuable antiscorbutic foods are orange, lemon, and pawpaw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Donaldson has recently reported upon the value of intravenous administration of orange-juice in serious cases of scurvy. For this purpose 15–35 c.c. of strained juice are neutralized with soda and made up to 60 c.c. with sterile saline. Of this mixture

15-20 c.c. are given every third day, and found to be sufficient ; it is said to be more efficacious than when given by the mouth.

Prophylaxis.—The prevention of scurvy consists in following the directions laid down, together with attention to oral hygiene. It has recently been pointed out that the main factor in the production of scurvy in native African races is the prolonged over-cooking¹ and steaming of food, especially of vegetables. It is, therefore, important that in gangs of unmarried natives efficient cooks should be appointed. As a general rule, the food cooked by native women is much more hygienic and palatable than that prepared by the men.

Wherever possible, in mines or tropical camps, native gardens should be established. Men threatened with scurvy should be given light work only.

¹ When cabbage is cooked for one hour at temperatures ranging from 80-100° C. the leaves lose 90 per cent. of their antiscorbutic value.

Section III.—ABDOMINAL DISEASES

CHAPTER XXII

CHOLERA

Definition.—An acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless serous material, by muscular cramps, suppression of urine, algidity and collapse, the presence of a special bacillus in the intestine, and by a high mortality.

History and geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal, and has from time to time spread as an epidemic over the rest of India. In 1817 it began to extend all over Asia, eastwards as far as Pekin and Japan, southwards to Mauritius, and westwards to Syria and the eastern shores of the Caspian. Stopping short at Astrakhan in 1825, it did not on that occasion invade Europe. Since 1830, when cholera first visited Europe, there have been at least five European epidemics—1848–51, 1851–55, 1865–74, 1884–86, and 1892–95. Minor epidemics have occurred in Europe since, but have been restricted in area. During the Balkan War of 1913, and in the course of the Great War, especially in the Balkans and in Mesopotamia, there were many outbreaks of cholera, but the disease did not extend as an epidemic beyond the actual seat of war.

The 1870–3 epidemic practically spared Great Britain, but it crossed the Atlantic and, entering by way of Jamaica and New Orleans, raged for a time in the United States.

From a study of the march of these epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) via Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) via the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) via the Red Sea, Egypt, and the Mediterranean.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings hundreds of thousands of human beings are collected together under highly insanitary conditions—as at the Hurdwar and Mecca pilgrimages. Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes,

infecting the people of places they pass through. In India cholera appears to spread from its home in lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did sixty years ago. On the other hand, isolated countries, such as the Andaman Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped.

Cholera in the main is a water-borne disease, the bacillus entering by the stomach. Several instances have been recorded in the literature which bear out this statement. But while ingestion of the bacillus is necessary to the production of cholera, it appears to be certain that this is not the only condition; possibly the state of health of the individual, or the degree of acidity of the gastric juice, renders some persons susceptible and others immune to the infection.

Rogers believes that the condition necessary for the spread of cholera in India is an absolute humidity of over 0.400, and that by watching the climatic conditions influencing the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time to enable steps to be taken to lessen its spread.

D'Herelle has made the interesting suggestion that the rise and fall of epidemics of cholera is due to the amount of bacteriophage produced. Patients in whose stools no bacteriophage appears die of cholera. Those cases in whom the bacteriophage is strong from the outset, rapidly recover. This substance, it is said, can also be demonstrated in well water.

Etiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease he examined. His observations have since been abundantly confirmed.

Description of the cholera bacillus.—The comma bacillus (Fig. 71) is a very minute organism, 1.5 to 2 μ in length by 0.5 to 0.6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—owing to their extreme tenuity are difficult to see in ordinary preparations. They

are not always present during the entire life of the parasite. In virtue of this appendage the bacillus exhibits very active spirillum-like movements. The individual bacilli when stained show darker parts at the ends or at the centre, suggesting spore-formation. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or it may happen that several bacilli are thus united, producing a spirillar appearance.

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the bacillus. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling

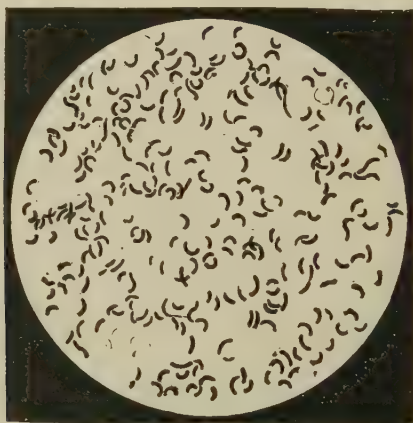


Fig. 71.—Cholera bacillus. Agar culture: 24 hours' growth. $\times 1,000$. (Muir and Ritchie.)

in milk. It dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of bacilli sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it the cultivations retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolytic if blood be added to the medium it grows on, such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c.

of a 5-per-cent. suspension of goat's corpuscles and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1-per-cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. The fermentation of lactose, with acid production, occurs two to three days later.

Although taken together, and in conjunction with the morphological appearance, these culture characters are fairly distinctive, nevertheless certain other vibrios, such as Finkler's spirillum, behave very similarly; and, as the morphology and behaviour of these paracholera organisms are very much like those of the cholera vibrio, a mistake is easily made. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1-per-cent. peptone solution.

The true Koch's vibrio may further be recognized by employing an artificial immune rabbit's serum, which will agglutinate the organism microscopically up to a titre of 1 : 12,000. This is the most satisfactory method of identifying the cultures, and is, in fact, the final test.

Is the comma bacillus the germ of cholera?—Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely, but, as they behave somewhat differently in the serological sense, they must be considered to be biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhoea has resulted, in only one case has true cholera been produced; furthermore, a few cases have been described which from a clinical point of view appear to be cholera, but in which the comma bacillus has not been discovered after a most careful bacteriological examination. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. By employing an "open bowl" method of enrichment of the faeces in a cholera district, Tomb and Maitra have been able to show that 35 per cent. of the inhabitants are chronic carriers of non-agglutinating vibrios, and they have proved to their satisfaction that the agglutinability is purely an artificial property developed and fixed in the organism by laboratory cultivation. When inseminated into water in a tank under natural conditions, agglutinating vibrios in cholera stools changed in twelve to fourteen hours to the non-agglutinating form. It is therefore possible that agglutinating vibrios are merely different phases of the same organism.

Toxins.—Filtered cultures of the cholera vibrio have little toxic action; the virus is apparently liberated by the disintegration

of individual organisms. Dead cultures, when given by the mouth, produce no effect, unless the intestinal epithelium is injured. The toxic bodies are mostly destroyed at 60° C.; when ground up and frozen by means of liquid air, an extract of high toxicity to laboratory animals, if injected intravenously, is obtained.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures of the vibrio. The blood-serum thus obtained shows marked agglutinative properties in a high titre towards cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose of organisms. When this happens, active bacteriolysis takes place, a phenomenon known as Pfeiffer's reaction. The test is performed as follows :—

A loopful of a young agar-culture of the vibrio is added to 1 c.c. of bouillon containing 0.001 c.c. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig; by means of capillary tubes inserted into the peritoneum the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into globules; if not, no change takes place.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents the shrunken and livid appearance already described. On opening the body, all the tissues are found to be abnormally dry. The muscles are dark and firm; sometimes one or more of them are discovered to be ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken; occasionally they may be congested and œdematous. The pulmonary arteries are distended with blood, the pulmonary veins empty. The liver is generally loaded with blood; the gall-bladder full of bile; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The outer surface of the bowel has generally a diffuse rosy-red, occasionally an injected appearance. On opening the bowel it is found to contain a larger or smaller amount of the characteristic rice-water material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregularly congested or arborescent patches of injection here and there throughout its extent.

If death occurred during the stage of reaction, the tissues are moist; the venous system is less congested; the lungs are probably congested and œdematous, perhaps inflamed. Very probably there are evidences of extensive enteritis.

Greig has shown that the gall-bladder and biliary passages are frequently

invaded by the cholera vibrio and that, as in the case of enteric, this viscus may act as a reservoir of infection (Fig. 72). Occasionally, according to the same authority, cholera may be a septicæmia; the vibrios have been demonstrated in the substance of the lung and kidneys, and in the spleen; they may be excreted in the urine (8 times in 55 cases—Greig).

On microscopical examination of the contents of the bowel during the acute stage of the disease the comma bacillus, in most cases, may be demonstrated. Usually it is in great abundance; occasionally it occurs in almost a pure culture in the upper part of the small intestine and duodenum, but it may be very rare in the large gut. Sections of the intestine show the bacillus lying on and between the epithelial cells of the villi and glands.

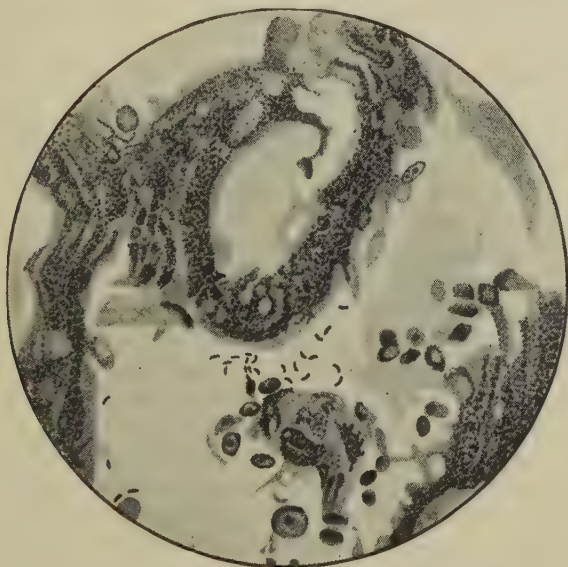


Fig. 72.—Cholera bacilli in gall-bladder. (After Greig, "*Ind. Journ. Med. Res.*")

Symptoms.—An attack of cholera commences in one of two ways: either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly and without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times an attack of this latter nature, after a day or two, may assume the characters of true cholera. The preliminary looseness in such cases is called the "premonitory diarrhœa." Whether this looseness is specially related to the subsequent attack, or is of an ordinary catarrhal or bilious type and acts simply by predisposing to the specific disease, has not

been determined. Possibly, owing to a catarrhal condition—in itself non-specific—the resisting power of the mucous membrane is impaired; possibly, in diarrhœa, the large amount of fluid in the gut affords a favourable medium for the cholera germ to multiply in. Besides diarrhœa, other prodromata, such as languor, depression of spirits, noises in the ears, etc., are sometimes noted.

When true cholera sets in, profuse watery stools, painless or associated with griping, and at first fæcal in character, pour, one after the other, from the patient. Quickly the stools lose their fæcal character, becoming colourless or, rather, like thin rice-water containing small white flocculi in suspension. Enormous quantities—pints—of this material are generally passed by the patient. Presently vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water description, supervenes. Cramps of an agonizing character attack the extremities and abdomen; the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions. The patient may rapidly pass into a state of collapse. In consequence principally of the loss of fluid by the diarrhœa and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's. The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow; the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then, after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal—to 93° or 94° F.; whilst that in the rectum may be several degrees above normal—101° to 105° F. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the “algid stage” of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the reappearance of the pulse at the wrist, and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, the secretion of urine returns, and in a few days the

patient may be practically well again. Usually, however, a condition known as the "stage of reaction" gradually supervenes on the algid stage:

Reaction: cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine may be secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidentally with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees of this reaction generally subside in a few hours; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, "cholera typhoid," ensues.

During the stage of reaction death may occur from a variety of complications—from pneumonia, from enteritis and diarrhœa, from asthenia, or from such effects of uræmic poisoning as coma and convulsions.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both as regards individual cases and as regards different epidemics. It is generally stated that during an epidemic the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

Ambulatory cases occur during all epidemics. Such cases are characterized by diarrhœa and malaise merely; there is never complete suppression of urine, the diarrhœa never loses its bilious character, and it is not accompanied by cramps. The attack gradually subsides without developing a subsequent stage of reaction.

Cholera sicca.—A very fatal type is that known as "cholera sicca." In these cases, though there is no, or very little, diarrhœa or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison, and dies in a few hours without purging or any attempt at reaction.

Hyperpyrexia is an occasional though rare occurrence in cholera. In such the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

Sequelæ.—Cholera is apt to be followed by a variety of more or less important sequelæ, such as anæmia, mental and physical debility, insomnia, pyretic conditions, chronic entero-colitis, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is

said to be of the gravest import. Pregnant women almost invariably miscarry, the foetus showing evidences of cholera.

Mortality.—The average case-mortality in cholera amounts to about 50 per cent. Some epidemics are more deadly than others. As already mentioned, the mortality is greater in the earlier than in the later stages of an epidemic. To the old, the very young, the pregnant, the subjects of grave organic disease—particularly of the liver, kidneys, and heart—the dissipated, the underfed, and the feeble, the danger is very great.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhoea, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is of importance to determine, correct diagnosis, though urgently required, may not be so easily attained.

Symptoms resembling true cholera may supervene in the course of an ordinary severe *diarrhoea*, and are very usual in cholera nostras, in mushroom poisoning, in ptomaine poisoning, in the early stages of trichinosis, and in a certain type of pernicious malarial fever. In none of these, however, is the mortality so high as in cholera. It may be laid down, therefore, that epidemic diarrhoea attended by a case-mortality of over 50 per cent. is cholera.

In other forms of diarrhoea it is rare for the stools to be persistently so entirely devoid of biliary colouring matter as they are in cholera. A careful inspection of the stools sometimes yields valuable information in other ways. Thus in mushroom poisoning, fragments of the mushrooms which caused the catharsis may be seen; in trichinosis the microscope may detect the adult trichina. In choleraic malarial attacks, the presence of the malaria parasite in the blood, the periodicity of the symptoms, their amenability to quinine, together with the character of the prevailing epidemic, generally combine to guide to a correct diagnosis.

The detection of the comma bacillus in the stools is now regarded as a positive indication of cholera. It would be rash, however, to affirm that a negative result from bacteriological examination of a single case is conclusive against its being cholera. Moreover, such examinations, to be trustworthy, have to be made by a skilled bacteriologist.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in faecal films stained by carbolfuchsin. According to Koch, a rough diagnosis may be made in 50 per cent. of cases by this method. If vibrios are very numerous, plates may be spread direct by means of a platinum loop on alkaline agar, or on Dieudonné's medium. When the vibrios are present in small numbers—(a) Alkaline peptone water should be inoculated with two or three loopfuls of the fluid stool and incubated for seven hours. (b) Any pellicle present on the surface of the broth should be examined in stained films or by means of the hanging-drop method. (c) If vibrios are scanty, reinforce by inoculating a second alkaline peptone tube and incubating for a further six to eight hours, and plate out on alkaline agar. (d) An emulsion of colonies from the plate or from an agar slope sub-culture should be agglutinated against the specific antiserum in high titre.

An agglutination of over 1:1,000 with a specially prepared serum is strongly suggestive of the true cholera vibrio, which may then be subjected to special biochemical tests.

The carrying out of the full technique of identification demands a considerable amount of time, and as promptness is the first essential in cholera diagnosis, be it of acute cases or of "carriers," other methods of rapid and more or less accurate diagnosis have been devised. Such a one is Bandi's method, which consists in inoculating the suspected faeces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, it is said that agglutination visible to the naked eye will be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum.

A modification of this method has been described by Davies in the rapid diagnosis of cholera cases and carriers, with satisfactory results. The advantages of such a rapid method are obvious: positive reports may be obtained on a large number of cases in as short a period as eighteen hours, and as many as 200 stools may be examined by one worker during the course of a morning's work. The following are the stages in the technique:—

1. Inoculate a platinum loopful of faeces into peptone water, 1-per-cent. peptone, 1-per-cent. NaCl, made distinctly alkaline to litmus.
2. Incubate for eighteen hours.
3. Place a drop of the resulting growth on the slab of Garrow's agglutino-meter (Appendix, p. 870), together with a drop of 1:80 anti-cholera serum. The resulting mixture will give a dilution of cholera serum 1:160. On the next partition drop an equal quantity of normal saline, together with a drop of the peptone culture, to act as a control. Rotate for three minutes. If vibrios are present a definite agglutination will be obtained. This can be confirmed later by agglutinating with cholera serum in still higher dilutions. It is recommended that stock bottles (with rubber caps) of cholera serum preserved with 0.5-per-cent. carbolic acid, in dilutions 1:80, 1:160, 1:320, 1:640, be kept. If an agglutination is obtained with the lower dilutions it may subsequently be titrated with the higher ones.

4. The peptone culture can then be spread with a platinum loop on Crendiropoulo's agar (alkaline agar), and a pure culture obtained by this means. The cholera colonies can easily be recognized by their transparent bluish-grey appearance. The hæmolytic and sugar tests may then be applied. It has been found that vibrios agglutinating with specific serum in high dilutions invariably give correct sugar, hæmolytic, and cholera-red reactions.

In an autopsy on a suspected case of cholera, at least two sections of the small gut, each about 5 in. in length—one just above the ileo-cæcal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline, and sent to a bacteriological laboratory as soon as possible for examination.

An agglutination reaction is not obtainable from the blood-serum during the acute stage, but it is present after eight to ten days from the commencement of the disease, reaching its maximum in four weeks; it may attain a titre of 1 : 1,000.

Differential diagnosis.—True cholera may have to be differentiated from *food-poisoning*, which may simulate it very closely, but in this instance there is usually a history of several persons having been attacked at the same time, after having partaken of a particular article of food, especially if it was tinned. It is said that leucocytosis is absent in food-poisoning and is usually found during the early stages of cholera. *Algid or choleraic subtertian malaria* may simulate true cholera very closely (see p. 41); *acute bacillary dysentery* may occasionally be so sudden and severe in its onset as to resemble cholera, while in *arsenical poisoning* vomiting is more usually the most urgent commencing symptom.

Treatment.—During cholera epidemics it is customary to establish depots where sedative and astringent remedies for the treatment of diarrhœa are dispensed gratuitously. Chlorodyne in small doses, 10–15 drops, has been found to be of value in staying the progress of the disease.

In the early stages of evacuation opium is of undoubted value. A hypodermic injection of morphia, $\frac{1}{4}$ gr. with atropine 1-100, should be given immediately. An anti-diarrhœic of proven value is as follows :

R̄	Sodi. bicarb.	.	.	.	gr. xv
	Cret. prep.	.	.	.	gr. xv
	Spir. ætheris.	.	.	.	℥ xv
	Spir. ammon. aromat.	.	.	.	℥ xv
	Tinct. opii.	.	.	.	℥ xxx
	Aq. chloroformi ad.	.	.	.	℥ i

of this, 1 fl. oz. should be given every twenty minutes till purging and vomiting cease.

Kaolin, or "bolus alba" as an intestinal astringent in large doses absorbs toxins, thus rendering them inert. It consists of kaolin¹ 200 grm. (7 oz.) in 400 c.c. (14 oz.) of water. This is a single dose, but if there is vomiting it may be repeated, and sipped in small amounts at a time. It is inconvenient to give on a large scale, on account of the bulkiness of the dose.

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated but not too cold room. His thirst should be treated by sips of iced water or of soda-water, or champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of germ and toxin. Cramps may be relieved by gentle friction with the hand or with ginger-root, by a small hypodermic injection of morphia, or, these failing, by short chloroform inhalations. The surface of the body should be kept dry by wiping it with warm dry cloths, and the surface heat maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Essential oils.—Tomb has introduced in the Asansol Mining Settlement, Bengal, a treatment of cholera by an essential-oils mixture, made up as follows:

R̄ Spt. æther.	.	.	.	℥ xxx
Ol. caryoph.	.	.	.	℥ v
Ol. cajup.	.	.	.	℥ v
Ol. junip.	.	.	.	℥ v
Acid. sulph. aromat.	.	.	.	℥ xv

One drachm, in half-an-ounce of water, every half-hour. Total average dose, 8 drachms.

This mixture should be given immediately, when practicable, but it is claimed that in 95 per cent. of cases recovery will be secured within a period of seven hours from the onset of symptoms. No special care need be paid to the subsequent dieting of the case. Vomiting, purging, and intestinal pains appear to be immediately controlled by the mixture. The value of the method in the mass treatment of natives is obvious, as little supervision is requisite.

For the stage of collapse which is due to the loss of a large

¹ Kaolin powder suitable for this purpose may be obtained from the Electric Osmosis Co.

amount of fluid from the system, intravenous injections of salines must be resorted to in order to restore the balance. The collapse in cholera does not differ fundamentally from collapse from hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of salt solution is therefore indicated. Normal saline solution, if given in sufficient quantities, acts well. Success appears to depend upon the introduction of a sufficient quantity. Three to four pints may be necessary. Should the veins be difficult to find, transfusion may be performed into the peritoneum or under the breast. After introduction of two to four pints of saline into the peritoneal cavity the veins soon become prominent and intravenous injection can be carried out.

Rogers's treatment.—Rogers, believing that collapse in cholera was due to excessive loss of chlorides from the blood-stream, introduced a method of treating cholera by intravenous injection of hypertonic saline solution. He claims that since the introduction of his method the case-mortality from this disease has been greatly reduced. Owing to collapse of the veins it is generally necessary to cut down on them in order to insert the cannula. The hypertonic solution is composed as follows : sodium chloride, 120 gr. ; potassium chloride, 6 gr. ; calcium chloride, 4 gr. ; sterilized water, 1 pint. The fluid in the containing bottle should be at a temperature of about 100° F. if the rectal temperature is below 99° F. ; if the latter is above 100° F., as there is risk from hyperpyrexia, the injection should be given at a temperature between 80° and 90° F. This solution Rogers introduces by means of a special stopcock cannula and transfusion bulb at the rate of not more than 4 oz. a minute, the flow being slowed down to 1 oz. if distress or headache supervenes. From three to six pints should be given if possible. At the same time Rogers gives potassium permanganate in solution or in pill by mouth up to 50 gr. a day as a means of destroying the toxins formed in the alimentary canal—2 gr. every quarter-of-an-hour for two hours, then every half-hour till the stools are coloured green. These pills are made up with vaselin and coated with salol.

With the intravenous saline Rogers combines hypodermic injections of atropine $\frac{1}{100}$ gr., morning and evening. The principles upon which the treatment is provided are as follows :

1. A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063 or over. In the acute stage of the disease the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.

2. A specific gravity of 1063 indicates a loss of half the fluid from the blood and, for correction, an injection of 3-6 pints.

3. The subsequent fall of blood-pressure to 70 mm. or under, or rise in the specific gravity to 1063, indicates repeated injections morning and evening.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle from 1048 to 1070. The specific gravity may be controlled by employing a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by means of a capillary pipette. A drop of blood which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

Cox of Shanghai has had encouraging results from continuous, prolonged, slow intravenous injections of isotonic saline fluid given by a special apparatus placed $2\frac{1}{2}$ ft. above the level of the patient's arm. The flow is kept up for several hours, at a rate of 2 oz. per minute, as long as there is danger from collapse. The saline injections may be combined with 5-per-cent. glucose, which may act beneficially in cases of urinary suppression.

In the stage of collapse, suppression of urine often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract is often useful during the stage of reaction. It is given in doses of $\frac{1}{2}$ to 1 c.c., injected hypodermically, two to four times a day; adrenalin may also be given, but its action is more transitory. Caffeine citrate 5 gr. is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. A mixture containing 5 min. of tincture of strophanthus given three times a day may be employed as an adjuvant. In cases of complete suppression, dry-cupping over the lumbar region morning and evening by means of Fenwick's cups is useful to re-start the flow of urine, and may be supplemented by hot dry fomentations. Rectal injections of hyperalkaline saline—150 gr. of sodium bicarbonate to the pint of isotonic saline—should be administered slowly every 2-4 hours in cases where collapse has been overcome, but suppression of urine persists.

During the stage of reaction, should purging persist, large doses of salicylate of bismuth with a little opium may prove of service. If the secretion of urine is not quickly restored, large hot poultices over the loins, dry-cupping of the same region, and the judicious use of bland diluents should be resorted to. Injections of digitalin, $\frac{1}{100}$ gr., may be given to stimulate the cardiac action. Retention of urine must be inquired about, and the region of the bladder frequently examined, and, if necessary, the catheter

employed. In the event of constipation, purgatives must be eschewed and simple enemata alone used.

In cholera convalescents the diet for a time must be of the simplest and most digestible nature—diluted milk, barley-water or rice-water, thin broths, meat juice, and so forth—the return to ordinary food being effected with the greatest circumspection.

Cholera typhoid must be treated much as ordinary enteric fever.

Nursing precautions.—It must never be forgotten by those responsible for the management of cholera cases that through their discharges such patients are a danger to the community, and that those discharges may contain the vibrio in some instances up to fifty days after the attack. Further, that though the germ dies in a few hours if dried, it preserves its vitality for many days if kept moist, as, for example, in damp, soiled linen; that it may live for months as a saprophyte in water or damp soil; and that it is not killed by ordinary cold. Therefore, all discharges and soiled linen from cholera cases should be immediately disinfected in a 2½-per-cent. cresol solution, or destroyed, and every precaution must be taken during convalescence, as well as during the acute stage, to prevent contamination of wells, public water supply, drinking and table vessels, and food.

Prophylaxis. Quarantine prevention.—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community; practically, it has proved a failure. Unless they are stringent and thoroughly carried out, quarantine regulations can be of little use. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from cholera, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools for as long as forty-four days. It was estimated that in the Naples epidemic of 1911, 90 per cent. of the cases were due to direct contact with patients or with healthy carriers; while in the Colombo outbreak in 1926, of 442 contacts examined, 10 per cent. were found to be carrier's of *V. cholerae*. For the recognition of the carrier state it is necessary, following the technique given at p. 371, to examine the stools of all contacts for the vibrio. A small dose of calomel to clear out the contents of the small intestine greatly increases the chance of recovering the specific organism from stools. This is the only scientific method of conducting a reliable quarantine.

The system to which Great Britain apparently owed her immunity during epidemics on the continent of Europe is a practicable

and, in civilized conditions, an efficient one. Under this system, only ships which were carrying or which had recently carried cholera patients were detained; and even these merely till they could be thoroughly disinfected. Thus inconvenience and loss to travellers and merchants were small, and the temptation to conceal cases of the disease or to evade regulations was proportionately minimized. Any cholera cases were isolated in suitable hospitals, the rest of the crew and passengers, although supervised for a time, being given free pratique. At the same time attention was not diverted from the sanitation of towns, especially of seaports—the measure mainly relied upon. Suspicious cases occurring on shore were at once reported to the sanitary authorities and promptly dealt with, fomites being destroyed or disinfected at as little cost and inconvenience to individuals as possible. Every endeavour was made to prevent faecal contamination of the public water supply.

Of late years, in India, preventive measures have been conducted much on the same lines, attention being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked after as far as practicable, special care being given to provide them with good drinking- and bathing-water.

Among the troops in India, on the appearance of cholera in their neighbourhood, special protective measures are promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Wells and water supplies during a cholera epidemic should be treated with potassium permanganate till the water becomes pink; an appropriate strength is 60 gr. to the gallon of water. The water should be left till colourless for twenty-four hours, and all vegetation and aquatic fauna removed.

Tomb's essential-oils mixture (p. 373), if administered in doses of 1 drachm in $\frac{1}{2}$ oz. of water daily, appears to be a good preventive. Its probable value is indicated by the fact that, under its influence, house infection (i.e. infection of other members of the household) appears to be obviated.

Incubation period.—All quarantine and protective systems must take cognizance of the fact that, although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days thereafter; three to six days may be set down as the usual duration of the incubation period.

Haffkine's inoculation.—During the Great War many millions of anticholeraic inoculations were made. The initial dose is $\frac{1}{2}$ c.c.

of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 c.c. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. The local reaction is, generally speaking, a very mild one. There may be œdema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, dark-ground illumination being employed. The emulsion is then heated to 55° C. for one hour, after which 1-per-cent. carbolic is added. The emulsion thus sterilized is finally diluted down so as to contain 8,000 million vibrios per c.c. of saline and 0·5-per-cent. carbolic.

The immunity thus produced does not seem to be a very persistent one, lasting at the maximum for three or four months.

Subsequent experience, particularly that obtained during the Balkan War of 1913, in Batavia in 1915 and 1916, and in the Great War, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

Immunization per os.—On the proposition enunciated by Besredka, vaccination by the mouth is now being practised in Russia, where the immunization of large numbers of people is necessary. It is premature to say whether this method is more effective than that outlined above. The vaccine is made from thick suspensions of the organisms killed by heat, carbolic acid, or alcohol, and given in from 3 to 5 doses ranging up to 100 c.c. every other day. Each dose consists of 10–100 milliards of vibrios, or 0·01–0·1 gm. of the dried organisms.

Personal prophylaxis.—During cholera epidemics great care should be exercised to preserve the general health; at the same time, anything like panic or apprehension must be sedulously discouraged. Fatigue, chill, and excess—particularly dietetic or alcoholic excess—are to be carefully avoided. Visits to cholera districts should be postponed if possible, seeing that the new-comer is especially liable to contract the disease. Unripe fruit, over-ripe fruit, shell-fish, food in a state of decomposition, and everything tending to upset the digestive organs and to cause intestinal catarrh, are dangerous. Melons, cucumbers, and the like deserve the evil reputation they have acquired. Purgatives—particularly saline purgatives—unless very specially indicated, should never be taken at these times. All drinking-water, and all water in which dishes and everything used in the preparation and serving of food are washed, should be boiled. Mere chlorination

of the water with bleaching powder (CaOCl_2) giving 1·3 parts of chlorine per million, or added to water in the proportion of 2 grm. of the powder to every 110 gallons, is not entirely reliable. Sodium bisulphate tabloids (2 grm. to $1\frac{3}{4}$ pints of water), by liberating sulphuric acid, provide a most useful method of sterilizing water for personal use, as for instance in a water-bottle. Filters—except perhaps the Pasteur-Chamberland filter—are not for the most part to be relied upon; in many instances they are more likely to contaminate the water passed through them than to purify it. A good plan in a household or in public institutions is to provide for drinking purposes an abundant supply of weak tea or lemon decoction, the supply being renewed daily; such a plan ensures that the water used in the preparation of the drink has been boiled. All food should be protected from flies. Diarrhœa occurring during cholera epidemics should be vigorously treated.

CHAPTER XXIII

THE DYSENTERIES

THREE types of dysentery, correlated to three different classes of parasites, are now definitely established. Though quite distinct, they are not mutually exclusive, for one type may be superimposed upon and complicate another; moreover, any or all of them may complicate some general disease, such as malaria or enteric. Henceforth, therefore, the term "dysentery" must be regarded as indicating a group of symptoms merely, and not a particular and etiologically distinct disease.

The principal forms of dysentery and their respective parasites are as follows:—

I. BACTERIAL—

BACILLARY DYSENTERY:

Bacillus dysenteriae Shiga and Flexner-Y.

II. PROTOZOAL—

AMOEBIASIS—Amoebic dysentery, Liver abscess, etc.:

Entamoeba histolytica.

BALANTIDIUM DYSENTERY:

Balantidium coli.

III. HELMINTHIC—

BILHARZIAL DYSENTERY:

Schistosoma mansoni, *S. japonicum*, or *S. hæmatobium*.

VERMINOUS DYSENTERY:

Cesophagostomum apiostomum.

I. BACILLARY OR EPIDEMIC DYSENTERY

Definition.—An acute epidemic disease due to invasion of the mucosa of the large intestine by a specific bacillus (*B. dysenteriae* Shiga and Flexner-Y). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa may take

place and quickly lead to death. In the milder forms the clinical symptoms may be those of a simple diarrhoea.

Geographical distribution.—Epidemics of bacillary dysentery have occurred at various times, both in the tropics and in temperate countries. At the present day such epidemics are of greater intensity and frequency in those countries in which the insanitary habits of the natives and more primitive conditions of life lend themselves to the spread of disease. In Europe, bacillary dysentery is to-day mainly an institutional disease, occurring not infrequently as outbreaks in lunatic asylums, prison camps, and military barracks.

Epidemiology.—In the tropics and subtropics, bacillary dysentery appears to observe a definite seasonal incidence. It is certainly prevalent during the rainy season and for a short period subsequent to this, but is most prevalent in the autumn months, while minor epidemics may occur in the early spring months as well. During the hot dry African summer the disease appears to be in abeyance.

Its spread from man to man takes place either by direct or by indirect contagion.

Large epidemics of bacillary dysentery occurred in all belligerents during the Great War, and as a cause of invaliding was hardly secondary to that of any other disease. In the East, the general tendency was to mistake, for reasons pointed out on p. 411, amoebic for bacillary dysentery. That bacillary dysentery was the predominating form in every epidemic was pointed out by the Editor in 1915.

Direct contagion by fæces can occur, as a rule, only among primitive communities in which the ordinary sanitary observances are either unknown or disregarded. Its occurrence and spread in lunatic asylums and Indian bazaars are attributable to personal habits which lend themselves to the spread of infection.

Indirect contagion. (a) *Flies.*—There appears to be little doubt that houseflies (*Musca domestica*) act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests.

In 1910 the Editor demonstrated dysentery bacilli, in considerable numbers, in the intestinal tract of houseflies taken in an endemic area.

The housefly is able to spread dysenteric infection in two ways—firstly, by its habit of regurgitation preparatory to feeding; and secondly, by its fæces. The latter is probably the more common. Buxton has found that the intestinal canal of the

majority of houseflies caught in Mesopotamia contains human fæces. One can therefore understand the importance of the insect in the spread of this disease as well as of several others.

(b) *Water* acts as a medium of infection, especially in the Malay States (Fletcher and Jepps). It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for so long a period if exposed to the sun or when associated with numbers of putrefactive micro-organisms.

Etiology.—*B. dysenteriae* was discovered by Shiga in 1897, and confirmed in the same year by Kruse in Germany.

TABLE SHOWING THE MORPHOLOGICAL AND CULTURAL CHARACTERS OF *BACILLUS DYSENTERIÆ* AND THE ALLIED GROUP OF MICRO-ORGANISMS AFTER TWENTY-FOUR HOURS' INCUBATION AT 37° C.

ORGANISM	MOTILITY	GLUCOSE	LACTOSE	DULCITE	SACCHAROSE	MANNITE	MALTOSÉ	INDOL	GELATIN	LITMUS MILK.
<i>B. typhosus</i> . . .	+	A	—	—	—	A	A	—	—	A
<i>B. paratyphosus-A</i> . .	+	AG	—	AG slowly	—	AG	AG	—	—	A
<i>B. paratyphosus-B</i> .	+	AG	—	AG	—	AG	AG	—	—	A later Alk.
<i>B. dysenteriae</i> (Shiga) .	—	A	—	—	—	—	—	—	—	A later Alk.
<i>B. dysenteriae</i> (Flexner-Y)	—	A	—	—	—	A	A or —	+ or —	—	A later Alk.
<i>B. enteritidis</i> (Gaertner)	+	AG	—	AG	—	AG	AG	—	—	A later Alk.
<i>B. faecalis alkaligenes</i> .	+	—	—	—	—	—	—	—	—	Alk.
<i>B. coli communis</i> . .	+	AG	AG	AG	—	AG	AG	+	—	A.C.
<i>B. acidi lactici</i> (Hüppe) .	—	AG	AG	—	—	AG	AG	+	—	A.C.

+ In motility column = presence of motility ; in indol = presence of indol.

± = variable; sometimes positive, sometimes negative.

— In motility column = absence of motility ; in gelatin = no liquefaction ; in indol = absence of indol ; in other columns = no change.

A = acid-production ; AG = acid- and gas-production ; C = clot in milk. Alk. = development of alkalinity.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length by 0.4 μ in breadth ; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity ; no spore-formation occurs. On agar and gelatin it grows as a thin smooth film with regular margins, and on agar and MacConkey plates its colonies much resemble those of the typhoid bacillus ; they are regularly round, light-blue in colour, and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, layer on potato. After a brief preliminary acid-production in

milk, it gives rise to a gradually increasing alkalinity. With solutions of the various sugars (*see* Table on p. 382) it produces acidity in glucose, but is inert in this respect in the rest of the series; it does not produce indol in peptone water. It is agglutinated in high dilutions by the serums of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the mucous stools of the corresponding period.

Varieties of Shiga's bacillus (resembling that organism in its sugar reactions, but forming indol and not agglutinating with Shiga-immune serum) have been described during recent years, but it is doubtful whether they are of etiological importance. They may possibly be secondary infections. Several species, that of Schmitz, of d'Herelle, the *B. ambiguus* of Andrewes, the para-Shiga +, or —, of Dudgeon, fall into this category.

Cultures of Shiga's bacillus are extremely toxic to laboratory animals, especially the rabbit. But in these animals they do not produce lesions characteristic of dysentery, though the filtered toxins, when injected intravenously, cause necrosis of the large intestine, on which they appear to exert some selective action. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

The causal relationship of the bacillus to disease is practically established.

Flexner's bacillus (the Flexner-Y group).—In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated from cases of dysentery in Manila by Flexner. Since that date a very large number of organisms belonging to this group have been described. Among the number may be cited the bacillus of Strong and the Y bacillus of Hiss and Russel, both of which at first were thought to differ in their biochemical and serological reactions, but this is now known not to be the case. From the work of Andrewes and Inman on a very large number of strains of the Flexner-Y—a mannite-fermenting group—it can be definitely stated that the organism does not adhere to one constant type, as does Shiga's bacillus, but differs greatly in the toxicity of the various strains and in their antigenic properties. The only basis for satisfactory sub-grouping is the serological method of Murray, Andrewes, and Inman. From their work it appears that five definite strains of the bacillus can be identified, termed respectively V, W, X, Y, Z, and for their recognition five specially prepared homologous serums are necessary. A pooled preparation of these five components is now obtainable for laboratory purposes and may be employed for the recognition of the bacillus.

Sonne's bacillus, an organism of this group, but which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere (Perry). The colonies tend to assume a much more crenated outline than do those of the true Flexner type. As a general rule cultures of Sonne's bacillus are not agglutinated by standard Flexner sera. When titrated against a specially prepared Sonne anti-serum agglutination to full titre occurs.

As a general rule, the dysentery bacilli can be isolated only from the intestinal canal. The organism has also rarely been obtained from the gall-bladder and from joint-effusions.

Apparently both the Shiga and Flexner bacilli are encountered in sporadic cases and in some epidemics without a preponderance of any one particular type; but it may be said that Shiga's bacillus is of more frequent occurrence in the tropics than in temperate zones, and that it is responsible for the most severe clinical forms of the disease, and consequently for the most virulent epidemics.

Pathology.—The earliest lesions of bacillary dysentery are confined to the solitary follicles of the large intestine, and result in a sinuous "snail-track" ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine, which eventually culminates in gangrene of the mucosa of the entire colon, as well as of the last 2–3 ft. of the ileum. Exceptionally the whole of the mucosa of the small intestine may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anal canal. In the stage of *necrosis* the large gut is contracted so as to resemble a rigid tube, and the mucous membrane is converted into a rigid, resistant, olive-green or blackish substance. (Plate XVIII, Fig. 2.) Its colour is thought to be due to the staining of the necrotic tissue by bile-pigments. Occasionally this necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of an acute toxæmia.

When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may involve the entire wall; such a bowel surface has a fenestrated appearance.

Chronic ulceration of the large gut in bacillary dysentery may occur. The smallest lesions are lenticular in shape and involve the mucous surface alone. The more advanced lesions amount to ulceration of limited tracts of mucous membrane, rarely penetrating below the muscularis mucosæ. Ante-mortem perforation of the gut may supervene, though it is extremely rare. For the differentiation of these ulcers from those of amœbic dysentery the reader is referred to the Table on p. 394.

These ulcers must also be distinguished from those of tuberculous, enteric, and bilharzial origin. In some chronic cases the mucous membrane may be entirely destroyed, rendering recovery impossible. The gut then resembles a piece of chamois-leather with interlacing fibrotic strands on the surface.

Mucous retention cysts, due to the formation of pseudo-adenomata from the bases of Lieberkühn's follicles, may sometimes be found as a sequela of bacillary ulceration. They may be recognized as jelly-like elevations forcing up the mucous surface and scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are probably present in the large intestine of "carriers" of the disease (Fletcher and Jepps).

Formation of granulation tissue.—Many cases of chronic bacillary dysentery acquired in the Great War showed no ulceration, but only a granular condition of the mucous membrane of the large gut. The lesions are distributed,



Fig. 1.



Fig. 2.

(P. H. Manson-Bahr, del.)

Fig. 1.—AMÆBIC DYSENTERY: Typical patches of infiltration and ulceration of ascending colon.

Fig. 2.—BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane.

INTESTINAL LESIONS IN AMÆBIC AND BACILLARY DYSENTERY. Half nat. size.

as a rule, in an irregular manner ; more usually confined to the lower portion of the large intestine. Considerable infiltration of the walls of the gut is associated with this condition.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round-cell infiltration. (Plate XIX.) The formation of large macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells, even in microscopic sections, are liable to be mistaken for *Entamæba histolytica*.

Symptoms.—After a short incubation period, usually of from one to seven days, as ascertained by experiment, the disease begins in a variety of ways, suddenly or insidiously, in all degrees of severity, varying from a mild diarrhoea to an acute fulminating choleraic attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, the frequent passage of loose, scanty, muco-sanguineous stools, often with dysuria.

The onset may be attended with high or moderate fever, or there may be no material rise of temperature. The symptoms may be grafted on to some general disease such as scurvy or malaria, or on to some chronic disease of the alimentary canal, as sprue ; they may assume acute characters, or from the outset they may be subdued in degree. As a general rule, the nearer to the rectum the lesions, the more urgent the tenesmus ; the nearer to the cæcum, the more urgent the griping. The general constitutional symptoms due to the absorption of toxins may be very marked. Vomiting may occur from the outset or be absent altogether.

Palpation of the abdomen can be effected only with difficulty during the early stages, owing to the protective rigidity of the recti. Later, especially in toxic and fatal cases, the abdomen may become quite lax and the spasmodically contracted sigmoid colon can easily be distinguished as an elastic coil under the examining hand. The implication of other portions of the large intestine can seldom be satisfactorily detected by a physical examination.

Character of the stools.—At first fæcal and diarrhoeic, the evacuations may vary enormously in number and character in the different types. Their number may be uncountable, the unfortunate victim being “glued to the commode.” At first, when they acquire definite characters, they consist of extremely viscid blood-stained mucus, which has been compared to “red-currant jelly” or “frog’s spawn,” and are generally odourless. The characters by which the exudation may be distinguished from the amœbic stool are given on p. 394. A few teaspoonfuls only may be passed at a time ; afterwards the stools contain less blood

and assume a more purulent character. Finally, the biliary pigments make their appearance, and the fæcal character of the stool may reappear.

In the most acute and fulminating forms the mucus may contain a large proportion of dark blood and resemble "meat washings." When necrosis of the mucosa has become finally established the stools may be exceedingly offensive, grey in colour, and contain much altered blood but no mucus.

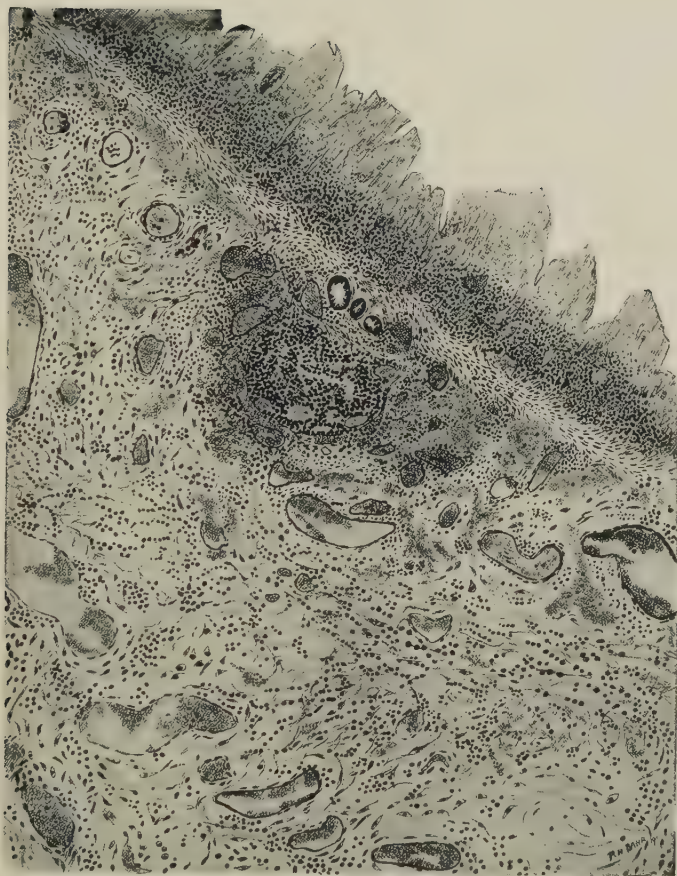
On clinical grounds, bacillary dysentery may be classified under various headings, as follows:

1. *Mild or catarrhal forms.*—A common history is that for some days the patient had suffered from what was supposed to be an attack of diarrhoea. The stools, at first bilious and watery, perhaps to the number of four or five in the twenty-four hours, had latterly and by degrees become less copious and more frequent, less fæculent and more mucoid, their passage being attended by a certain amount of straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The whole attack may be over in a week, and the stools may not number more than twelve in the twenty-four hours. The majority of these mild cases are due to Sonne's bacillus.

2. *Acute bacillary dysentery.*—In another type of case the onset is much more abrupt. Within a few hours of its commencement the disease may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by most distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious and pinched, the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began. (Chart 30.)

3. *Fulminating bacillary dysentery.*—The attack generally begins suddenly, it may be in the middle of the night, with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, collapse sets in with a subnormal temperature, and the patient dies. So virulent may be the toxæmia



**MICROSCOPICAL SECTION OF LARGE INTES-
TINE IN BACILLARY DYSENTERY.**

Showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa. (*P. H. Manson-Bahr, del.*)

that death may take place before dysenteric stools are emitted. The tongue is thickly coated, and all the other symptoms of an acute toxæmia are present. The abdomen is sunken and acutely tender. The stools rapidly assume a liquid, offensive character, and are of a greenish or greyish hue. Towards the end neither blood nor mucus may be visible in the stools, whilst in number they may be uncountable.

A *choleraic* form, in many respects resembling cholera, has been noted; these cases are by no means frequent. The onset is acute, with vomiting. Collapse with its attendant phenomena sets in early, and the stools may consist of a watery substance alternating with liquid blood-stained mucus or, it may be, almost

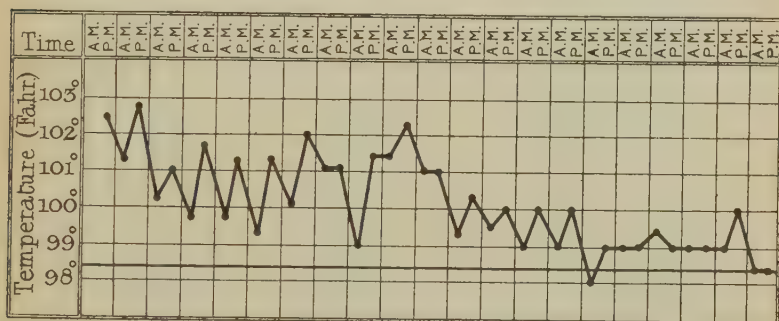


Chart 30.—Bacillary dysentery. (Orig.)

pure serum. The temperature is subnormal, and death takes place within three days.

4. *Relapsing bacillary dysentery*.—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, symptoms do not completely disappear. The stools may recover their fæculent character, or may even show some signs of formation yet they continue to be passed too frequently, are often preceded by griping, and contain a variable amount of muco-pus with or without blood. Bacillary cases of this type may be due to a fresh infection or to a lighting up or recrudescence of an old focus.

5. *Chronic bacillary dysentery*.—In quite a large proportion of cases of acute dysentery the fæces do not become absolutely normal for a considerable time after the abatement of the more urgent symptoms. On the slightest indiscretion, either of food or of drink, the old symptoms reappear. In such cases sudden attacks of diarrhœa are common. For months, or even years, some patients never pass a perfectly healthy stool, the uniform

motion always containing slime or muco-pus, and at times blood. Often there is a tendency to scybalous stools, or to constipation alternating with diarrhoea. The clinical appearance of these cases is almost characteristic, and the state has been described as the *Morbus bengalensis*.

Since the end of the Great War a form of chronic bacillary dysentery has been recognized which differs materially from any previously described. As a general rule, the initial attack may have been so mild that it has passed unnoticed, but recurrence of symptoms takes place, with passage of blood and mucus, becoming more frequent and severe year by year. Eventually the stool consists of little else than large quantities of blood-stained mucus and necrotic epithelium. The course of these cases is invariably progressive, and, unless vigorously treated, they terminate fatally. Emaciation may be extreme, especially in native races; an adult man may weigh less than $3\frac{1}{2}$ stone (Fletcher and Jepps). Considerable anæmia may develop, with cardiac failure and dropsy. Death may ensue from exhaustion, or from some intercurrent disease such as phthisis or malaria.

Post-dysenteric ascites.—Megaw is of the opinion that the ascites which is so common in most hospitals in India is a sequel to bacillary dysentery. When bacillary dysentery is not treated, or is improperly handled, the dysenteric toxins pass through the intestinal wall and set up an irritative peritonitis which is followed by fibrosis of the peritoneum. The result is an accumulation of ascitic fluid. There is no associated cirrhosis of the liver.

Predisposing causes.—Bacillary dysentery is especially apt to attack those who are in an enfeebled state of health owing to starvation, unsuitable dietary, physical exhaustion, or exposure, or whose health has been undermined and resistance lowered by some chronic disease such as malaria, tuberculosis, scurvy, or enteric. In the feeble-minded, in very young children, in the aged, and in pregnant women, bacillary dysentery is apt to assume a serious and toxic form. Young children may show pronounced symptoms of toxæmia, and die in convulsions or in coma.

Complications.—*Dysenteric rheumatism*, as it has been called, has long been known to Indian practitioners. An effusion into the cavity and ligaments surrounding the joints, especially the knee and ankle, may come on during the acute stage of the disease, or, as is more generally the case, during convalescence when the stools are more or less fæculent. (Fig. 73.) It is common in some epidemics, in others it is absent. It is most frequent in Shiga infections. A considerable pyrexia accompanies the joint-effusions.

The condition may last a considerable time, but usually clears up without leaving any permanent deformity, though, exceptionally, permanent disability may result. The fluid from the joints is sterile,¹ and will agglutinate the dysentery bacillus (Klein). This condition has to be distinguished from fugitive serum-arthritis, such as often occurs after the injection of anti-dysenteric serum.



Fig. 73. — Arthritis of hands and knees in bacillary dysentery.
(Photo : Dr. G. Hall.)

Eye complications, etc — Both acute *conjunctivitis* and *iridocyclitis* are now regarded as symptomatic of dysenteric toxæmia. The former is frequently noted as a complication in association with arthritis, whilst iritis occurs only in a small percentage of cases. Parotitis, either unilateral or bilateral, has been observed, and is possibly due to septic absorption from the mouth. Intus-

¹ Shiga's bacillus has been isolated from the fluid in one instance (Elworthy).

susception of the large or the small intestine has been found in children, and is in them a common terminal event in acute cases.

That the eye and joint complications referred to are due to an endotoxin is indicated by experimental work on animals. This shows that the filtrates of Shiga cultures, when injected intravenously, lead to the production of iritis and arthritis, as well as of local lesions in the cæcum.

Bacillary-dysentery carriers.—A carrier state supervenes in about 3 per cent. of recovered cases of bacillary dysentery. By the term carrier is meant a condition in which the specific bacilli continue to be excreted in an otherwise normal stool.

Carriers of the Flexner-Y bacillus are much more frequent than carriers of the Shiga bacillus. Generally the average Flexner carrier is in good health, while the Shiga carrier is usually an invalid. According to Fletcher, carriers are seldom encountered after the ninth month subsequent to recovery from the initial attack of dysentery.

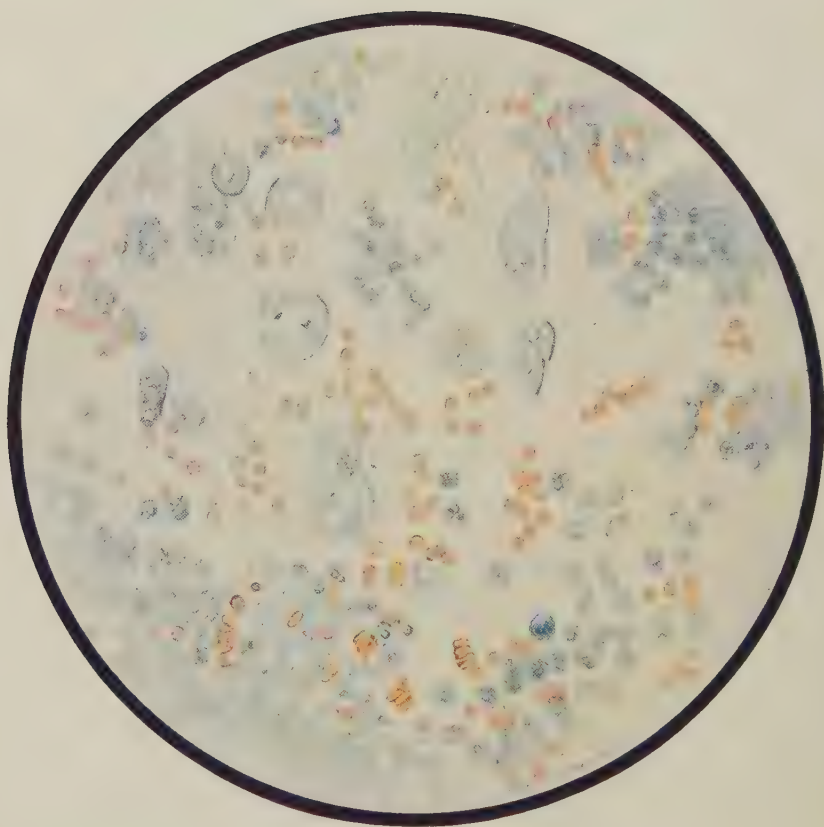
There is a condition in which bacillary inflammation or ulceration is localized in the lower portion of the rectum; patients often involuntarily pass viscid mucus, though otherwise in good health, and the bacillus may be isolated after a lapse of three years from the initial attack.¹

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible a laboratory diagnosis should be made.

The possibility of malaria occurring in the course of bacillary dysentery should always be borne in mind. Dysentery very often awakens a latent malaria; this is frequently the case in the benign tertian form. The concurrence of a subtertian infection with bacillary dysentery is a particularly serious combination.

Generally, a tentative diagnosis may be made from a microscopic examination of the *cellular exudate* in the stools—that is, if the distinctive cellular picture is obtained, a method now known as cyto-diagnosis. For this purpose the specimen should be procured fresh from the patient and as early as is possible in the disease. The characteristic feature of the bacillary stool, as seen under the microscope (Plate XX), is the preponderance of swollen *polymorphonuclear leucocytes*, with distinctive ring-like nuclei; they constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a $\frac{1}{8}$ -in. lens and a low ocular ($\times 2$).

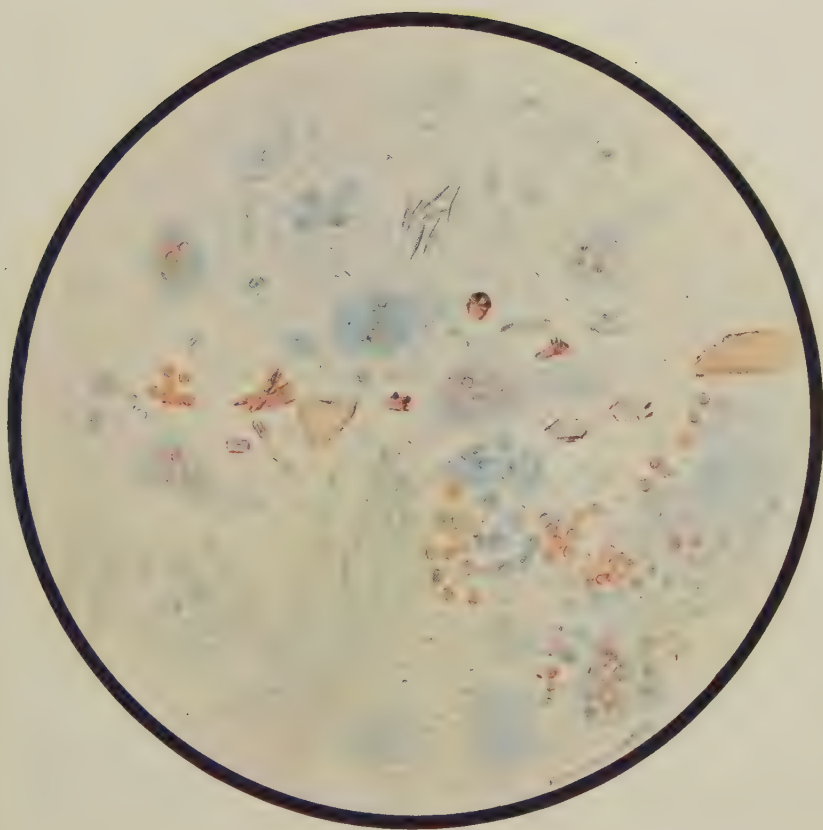
¹ Simple microscopic examination of the fæces affords little assistance in these cases. The chances of isolating the specific bacillus are considerably increased by making cultures direct from the mucosa by rectal swabs, or from scrapings of ulcers obtained through the sigmoidoscope.



**MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE
IN ACUTE BACILLARY DYSENTERY (Shiga infection).**

Fresh preparation. Shows macrophage cells with ingested red blood-corpuscles, intestinal epithelium and polymorphonuclear leucocytes.

PLATE XX



MICROSCOPIC APPEARANCE OF EXUDATE IN AMÆBIC
DYSENTERY.

Fresh preparation. Shows active *Entamæba histolytica*. Some with ingested red blood-corpuscles, acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

Macrophage cells.—These cells, sometimes 20–30 μ in diameter, are apparently derived from a proliferation of the endothelium of the capillary vessels of the gut. In shape they may be round, oval, or even bilobed. (Plate XX.) They are hyaline in appearance, and contain in their substance vacuoles and fatty granules, ingested red blood-corpuscles, or even occasionally leucocytes. They are non-motile, but, owing to their phagocytic activities, are apt to be mistaken for *Entamoeba histolytica*—an error often made by the inexperienced.

It appears to be more important than ever that the significance of macrophage cells in bacillary dysentery stools should be emphasized. The tendency to diagnose amœbic dysentery upon a shred of evidence is very pronounced. It is most important that the pathologist should acquaint himself with the appearance of inflammatory cells which appear in the fæces as well as with the different stages of the dysentery amœba, before an expert diagnosis can be given. The main features of the cyto-diagnosis of dysentery stools was pointed out by the Editor in 1912 and this method was practised by him during the Great War at which time it received ample confirmation.

Entamoeba coli and the flagellate protozoa (*Chilomastix* and *Trichomonas*) may be present in considerable numbers in a bacillary-dysentery exudate, especially during the convalescent stages. Difficulty may be experienced in differentiating *E. coli* from *E. histolytica* in a bacillary-dysentery stool, and may lead to the suspicion that one is dealing with a double infection of two diseases.

Cutaneous reaction.—An intradermal cutaneous reaction on the lines of the Schick test and the “Melitene” reaction has recently been described. For this purpose 0.1 c.c. of 3-per-cent. saline solution of standard Shiga toxin (lethal to rabbits in doses of 0.1 grm. per kilo of body-weight) is injected intradermally, and produces in healthy persons, after several hours, an inflammatory oedematous area. Negative results are obtained in those previously injected with anti-dysenteric serum or those who have previously suffered from bacillary dysentery.

Isolation of the dysentery bacillus.—With practice this becomes a comparatively simple matter. The stool should be collected in a bed-pan, which should contain no disinfectant, and the patient should be warned against passing urine at the same time; a portion of freshly-passed blood and mucus should be picked out of the mass by means of a platinum loop, and, if soiled with fæces or urine, should be shaken up in 5 c.c. of distilled water or normal saline solution. The earlier in the course of the illness, the easier it is to isolate the dysentery bacillus. It is, as a general rule, difficult to do so after the dysentery has lasted five days. The explanation of this phenomenon appears to lie in the production of d’Herelle’s bacteriophage which is inimical to the further multiplication of the dysentery bacillus. It must be remembered that the organism is very delicate, and never occurs

in great profusion even in a freshly-passed stool. The mucous, or two loopfuls of the suspension, should be spread, in a spiral manner, somewhat thickly upon a MacConkey agar plate; some prefer Conradi-Drigalski, others plain litmus-lactose agar, for this purpose. A preliminary incubation of the specimen in MacConkey's broth is not to be recommended, as the dysentery bacillus is so easily overgrown by other organisms of the *Bacillus coli* group.

The plate, spread in this manner, should be incubated at 37° C. in an inverted position for eighteen hours, and the small blue transparent colonies then examined with a watchmaker's lens. As a general rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Y group. In order to make their recognition still easier, it is a good plan to hold a finger or a piece of dark paper against the back of the plate. In sending specimens for laboratory examination through the post, or by messenger over long distances, the fæces should be emulsified with a double volume of 30-per-cent. glycerin in 0.6-per-cent. saline solution (Teague and

Clurman), or, better still, with an equal volume of $\frac{N}{33}$ NaOH solution which,

by rendering the medium alkaline, conserves the vitality of the organisms for a longer period (Dudgeon).

Identification of the colonies may be carried out as follows: Four or more should be picked off with a platinum spud and transplanted on to agar slopes, and, after a suitable incubation period, these subcultures should be emulsified and tested in high dilutions against specific anti-Shiga and anti-Flexner-Y serums in agglutination tubes. Should the method of macroscopic agglutination be utilized, these serums will be found very specific, so that either on a microscope slide or on the agglutinator (p. 870) agglutination rapidly occurs.

As a measure of practical importance, a method of preliminary agglutination may be employed. Ten or more suitable colonies are picked off the plate by a platinum spud or small loop, and emulsified in a very small quantity (0.25 c.c.) of normal saline; a rather thick opalescent emulsion results. By means of a capillary pipette, drops of this emulsion are placed together with an equal quantity of the specific serums diluted to 1:50. The resulting dilution of the serums will then be 1:100. The test may be performed either on a microscope slide or on the agglutinator. After oscillation for three minutes, should the reaction be positive, snowflake agglutination occurs.

After these preliminary measures the diagnosis may be confirmed by inoculating subcultures of the organism into the sugars (Table, p. 382).

Isolation of the dysentery bacillus post mortem.—The bacillus can be isolated with ease from the acutely inflamed mucosa by washing the canal free from intestinal contents and scraping off the blood and mucus with a platinum loop. From the mucosa which has undergone coagulation necrosis this is by no means easy. In this case the surface must be first seared with a hot knife or glass and incised; the material for culture is then obtained with a platinum loop from the bottom of the incision.

The bacillus may occasionally be recovered from the inflamed mesenteric glands, but not from the bile, liver, spleen, or any solid organ.

Serological diagnosis.—This is of little value as an aid to diagnosis in the early stages of the disease, or in the very acute or rapidly fatal types in which it is so important to arrive at an accurate opinion. The serums of some patients, proved to be suffer-

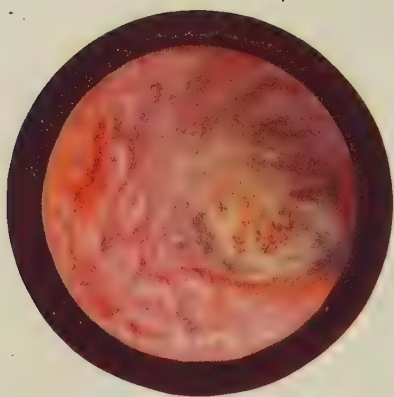


Fig. 1.—Acute bacillary dysentery (Shiga infection). Note œdema of mucosa and submucosal hæmorrhages.

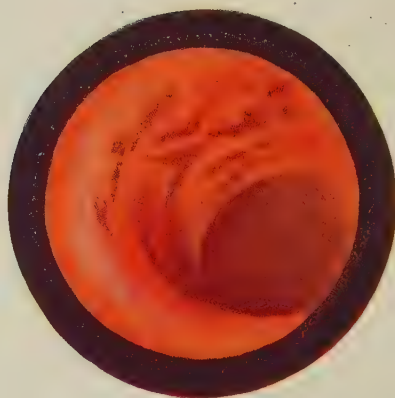


Fig. 2. Chronic bacillary dysentery (Flexner infection). Note granulations on mucous membrane.

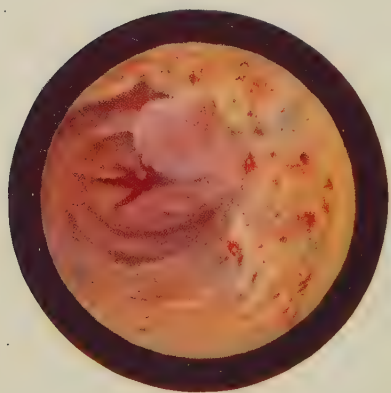


Fig. 3.—Acute amœbic dysentery. Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

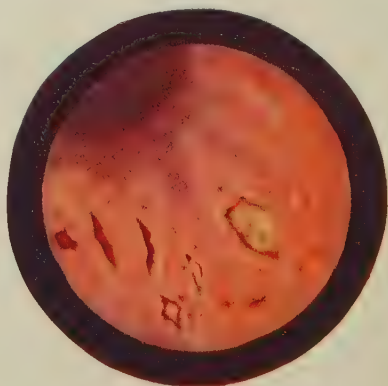


Fig. 4.—Chronic amœbic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

(P. H. Manson-Bahr, del.)

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMŒBIC DYSENTERY.

ing from bacillary dysentery by isolation of the specific organisms from the stools, may give a negative agglutination reaction, and, further, certain normal serums have the power of agglutinating the bacilli in low dilutions.

For the diagnosis of Shiga infection, say in convalescent or chronic cases, an agglutination of over 1 : 25 should be obtained. In Flexner infection an agglutination of 1 : 100 is sufficient for a positive diagnosis.

Sigmoidoscopic examination.—The sigmoidoscope is especially useful in chronic cases, and should be employed wherever practicable. For preparation of the patient, a cathartic of $\frac{1}{2}$ oz. of castor oil is given the previous evening; the following morning the bowel is cleared out by means of a soap-and-water enema. It is advisable to give 10–15 min. of tincture of opium half-an-hour before the examination, in order to render the patient less sensitive. The mucous membrane of the rectum is seen to be replaced by granulation tissue with surrounding hyperæmia which has a characteristic appearance resembling the cortex of a granular kidney after the capsule has been stripped; at the same time infiltration and thickening of the bowel-wall can be made out. (Plate XXII.) Seldom are ulcerations seen in chronic cases. The passage of an instrument is attended by very great pain, which in itself is almost diagnostic, as amœbic ulceration of the bowel is almost entirely non-sensitive.

DIAGNOSIS BETWEEN BACILLARY AND AMÆBIC DYSENTERY

BACILLARY DYSENTERY

An acute disease with a tendency to epidemic spread.

Incubation period a short one, 7 days or less.

Onset acute.

Pyrexia common.

Course days or weeks.

Complications: No hepatic symptoms; polyarthritis frequent.

Death due to—

(a) Exhaustion.

(b) Toxæmia.

Signs: General tenderness over whole abdomen, more marked over sigmoid flexure.

Tenesmus very severe.

AMÆBIC DYSENTERY

A chronic endemic disease.

Incubation period a long one, at least 20–90 days, it may be more.

Onset insidious.

Pyrexia rare, unless complicated.

Course usually prolonged.

Complications: Hepatitis, abscess of liver, abscesses more rarely in other situations.

Death due to—

(a) Exhaustion.

(b) Perforation.

(c) Hæmorrhage.

(d) Liver abscess.

Signs: Local tenderness and thickening, mostly over sigmoid flexure transverse colon, and cæcum.

Tenesmus not accentuated.

DIAGNOSIS BETWEEN BACILLARY AND AMÆBIC DYSENTERY
(Continued)

BACILLARY DYSENTERY

Pathology : Acute diffuse necrosis of mucous membrane of large intestine, due to toxins of the dysentery bacillus.

Ulcers : When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.

Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers; bases consist of granulation tissue.

Intervening mucous membrane hyperæmic. Rarely perforate. No compensatory thickening of bowel-wall.

Stools : Scanty; many in number. Bright blood-red, gelatinous, viscid mucus, odourless, resembling red-currant jelly.

Reaction ; Alkaline.

Microscopic picture : Numerous red cells; polymorphs numerous, with clear-cut ring nuclei. Macrophage cells may be numerous. Few visible micro-organisms. (Plate XX.)

Blood examination : No leucocytosis.

AMÆBIC DYSENTERY

Pathology : Local lesions confined solely to the large intestine, due to the characteristic ulcers.

Ulcers : Commence as small abscesses of submucosa, distributed in long axis of gut.

Oval in shape, regular in outline; flask-shape in section, involving all coats; bases consist of necrotic black tenacious sloughs.

Not uncommonly perforate; compensatory thickening of bowel-wall. Intervening mucous membrane not affected.

Stools : Fæces intermingled with blood and mucus, resembling anchovy sauce. Very offensive, smelling of decomposing blood; generally copious.

Reaction ; Acid.

Microscopic picture : Red cells numerous and in clumps, polymorphs much damaged, often extruded nuclei. Macrophage cells scarce. Large numbers of motile bacilli, *Entamoeba histolytica*, generally with ingested red cells. Charcot-Leyden crystals common. (Acton and Thomson.) (Plate XXI.)

Blood examination : Usually a moderate leucocytosis.

Prognosis depends very much upon the susceptibility and physical condition of the person attacked. In the jails of India, in fact throughout that country, though bacillary dysentery is widespread, the case-mortality is very small indeed. Of the many thousands of cases among British troops in the Great War, it is doubtful whether the case-mortality at any period rose above 5 per cent. Epidemics have been recorded in which the mortality was over 28 per cent., and others among debilitated natives, as, for instance, Solomon Islanders, in which the death-rate was 47 per cent. Prognosis is bad in the chronic cases; especially is this the case in poverty-stricken, malaria-infected, half-starved natives.

Treatment.—The patient should be placed in bed on the appearance of the first signs, and should on no account be permitted to get

up in order to pass his motions. A bed-pan should therefore be employed wherever nursing facilities are available. In the choleraic or fulminating cases in which the passage of stools is incessant, and the physical exhaustion consequently very great, it may be advisable to dispense with a bed-pan altogether. The patient should be placed upon a waterproof sheet and the buttocks well padded with tow, which, when soiled, can be collected and burned. For this purpose the attendant, for self-protection, should wear rubber gloves.

Arrangements should be made for the periodic inspection of the stools, for by these, supplemented by the appearance of the tongue and the general condition of the patient, the progress of the case can best be ascertained.

Considerable attention should be paid to the diet, which should be nutritious and easily assimilable, leaving as little residue as possible. Modern medical opinion is strongly opposed to milk in the routine treatment of bacillary dysentery. Whether plain, boiled, or peptonized, it is apt to curdle in the intestinal canal, and the casein clots thus formed have to be passed in the stools. The best diet is one consisting of jellies, albumen water, rice water, chicken conjé, beef tea, Brand's essence, arrowroot, sago puddings, any of which may be given at two-hourly intervals in small quantities (6-10 oz.), slightly warmed, at each feed. The physical exhaustion necessitates a nutritious diet ; it is therefore inadvisable to attempt to feed dysenterics over a long period on albumen water alone.

In all cases alike, even in the severest, treatment should be preceded by a mild purge ; the most suitable one for the purpose is castor oil, to which tincture of opium (15 min.) may be added. The routine treatment with saline aperients has received general commendation. The best salt for the purpose is sodium sulphate in drachm-doses exhibited two-hourly for the first day or so, afterwards every four hours until the stools become fæculent. Some clinicians prefer routine treatment with castor oil, which is given in drachm-doses hourly for eight doses till the third or fourth day of the illness ; subsequently saline purges are given.

Opium.—It is permissible to exhibit opium, either by the injection of morphia or in solution, as a means of promoting sleep and relieving pain if very severe.

Bolus alba.—As a means of checking the diarrhoea and of eliminating the dysentery toxins in the intestinal canal, a mixture of animal charcoal and kaolin has been utilized in Germany and in Austria ; the powder should be given suspended in water in doses of three teaspoonfuls every few hours.

Yatren, given in pill form by the mouth or injected per rectum, is said in Germany to be a most useful drug (p. 417).

Anti-dysenteric serum,—The best-known serums are those prepared by the Lister Institute; similar serums are made by Mulford, the Berne Institute, by Shiga in Japan, and Dopter in France. The action of the serum is to be regarded as purely antitoxic rather than antimicrobial. The idea underlying its administration is that of neutralizing the toxæmia and of preventing, if possible, cellular necrosis of the mucosa. When necrosis has occurred, it is doubtful whether the serum has any effect whatever. Not every case of bacillary dysentery requires antiserum treatment. The indications for the injection of serum should be based upon a consideration of the patient's condition, the number of stools, the pulse, and the abdominal pain. An indication for prompt serum treatment is pyrexia, with the passage of more than twelve to eighteen stools in the twenty-four hours.

There are various routes by which the serum may be administered. In very severe or fulminating cases it is best given *intravenously* by the open method, in doses of 50–60 c.c. diluted with a pint of saline. The fluid should be injected slowly, at least ten minutes being spent in the process. It is advisable to warm the diluted serum to 99°–100° F. before injection, and, if a deposit is present, to strain it through a piece of linen which has been boiled, or through sterilized filter-paper.

Owing to the possibility of hypersensibility (anaphylaxis) to horse-serum developing—which, though occurring rarely, may be attended by fatal results, especially after intravenous injection—it is advisable to inquire whether horse-serum has been administered to the patient at some previous period.

Either the median cephalic or the median basilic vein should be chosen. The veins can be made prominent by means of a rubber bandage, or even by digital pressure. It is unnecessary to incise the skin. If a larger quantity has to be introduced than the syringe will hold, as is generally the case, one can disconnect the barrel, leaving the needle in the vein, and, by placing the finger gently upon the vein, exclude any air while an assistant refills the barrel.

The serum is absorbed much more quickly by the *intramuscular route* than when given subcutaneously, the time for the former being eight as against forty-eight hours. A convenient site is the adductor muscles of the thigh; the needle should be inserted at a point well internal to the femoral artery. A large-bore needle should be used, and every aseptic precaution observed.

The sites generally chosen for *subcutaneous injection* are the

flank, between the crest of the ilium and the costal margin, or the lax tissues over the lower part of the abdomen. The pain which results from the distension of the tissues when 100 c.c. or more are given constitutes a disadvantage of this method. Whichever route is chosen, if the toxic symptoms do not abate, a second injection may be given forty-eight hours after the first.

In children, who become rapidly poisoned with dysenteric toxins, the *intraperitoneal route* is recommended. The serum, 10-30 c.c., should be diluted with 150 c.c. of 5-per-cent. glucose in normal saline solution.

Care must be taken that the serum does not deteriorate after long storage. In the tropics all curative serums should be stored in the ice-chest.

A week or so after the injection, *serum sickness* is apt to supervene. An urticarial rash is accompanied by pyrexia, malaise, and stiffness of the joints. To anticipate and prevent the advent of these symptoms, it is recommended that calcium lactate (20 gr.) should be given by mouth on the day of the injection and on two or three subsequent days.

Serum treatment is of little avail in the chronic form of the disease or in greatly debilitated natives.

Bacteriophage.—It is probable that natural recovery from an acute attack of bacillary dysentery lies in the production of a corresponding amount of bacteriophage in the intestinal canal to combat the infection. This has led to the interesting speculation as to whether bacteriophagic substances, as say, an anti-Shigaphage, might not be used in treatment. Treatment by the administration of bacteriophage by the mouth is now being carried out in various parts of the world, and the result will be awaited with interest.

Relief of pain.—During the early stages of an attack the patient may suffer much from griping and tenesmus. These are generally relieved by a hot bath, or by hot fomentations, or turpentine stupes; three or four of them may be roughly sewn into a piece of flannel and laid on the abdomen. This application has the advantage of being very light, of not wetting the clothes, and of keeping warm for many hours. Tenesmus and dysuria are best relieved by morphia hypodermically; or by an enema of a wineglassful of thin starch containing 40 or 50 drops of laudanum; or by suppositories of morphia and cocaine. Washing out the rectum with a pint of very hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, of mitigating, the incessant desire to go to stool and to strain. Bismuth 2 dr., with

laudanum 30 min. and thin starch 2 oz., is also a good sedative enema.

Collapse may occur at almost any stage, and may be due to physical exhaustion caused by excessive straining and loss of fluid. Every endeavour should be made to restore the balance by the intravenous injection of large quantities of saline and glucose.

Vomiting and hiccough in these severe cases should both be regarded as of serious portent.

Treatment of complications.—*Arthritis* is best treated by application of Scott's dressing, by radiant heat, or by sand-baths at 45°–60° C.

When the joint is greatly distended the excessive fluid may be aspirated. *Iritis* is treated by atropine, the use of an eye-shade, etc.

Treatment of chronic bacillary dysentery cannot be considered very satisfactory, for the healing of a chronically scarred and ulcerated bowel is effected slowly and with difficulty. The diet should be carefully regulated, and small doses of aperient salines given at regular intervals. Gentle abdominal massage over the course of the large intestine, in order to promote normal peristalsis, may assist in relieving pain and in promoting the nutrition of the gut-wall.

Rectal irrigation.—Apart from operative measures, described below, the most hopeful method of treating the chronic form of the disease is to irrigate the affected surface of the large bowel with various antiseptics, with the object of cleansing the gut and stimulating the processes of repair. The following apparatus is required:

Fig. 74.—Funnel and rectal tube for intestinal lavage.

- (1) A glass funnel, which should be cylindrical in shape, 1½ in. in diameter, and so graduated as to hold 10 oz. of fluid. The lower part should be provided with a constriction so as to accommodate the rubber tubing and to afford it a firm grip. The tubing itself should be bound round with a tape ligature.
- (2) Rubber tubing ½ in. in diameter; a length of 3 ft. is required.
- (3) Rectal tube. This should be a stout catheter at least ⅜ in. in diameter, with a big round terminal opening.
- (4) A bulbous glass connecting tube (Fig. 74) for joining the tubing to the rectal tube.

- (5) Narrow tape, necessary for tying securely all the junctions.
- (6) Rubber gloves for the operator's hands, and a supply of vaselin.

Methods of administering the lavage.—The patient should be given ½ oz.



of castor oil subsequently to his ordinary meal the previous evening, but on the morning of the irrigation only a light breakfast should be permitted. A large enema of sodium bicarbonate solution (1 dr. to the pint) should be given to clear out the bowel about half-an-hour before the irrigation is due. The apparatus should then be fitted together, securely tied, and sterilized. The temperature of the fluids used for irrigation should be 100–110° F.

When the patient is reasonably robust, the irrigation can best be administered in the genupectoral rather than in the right lateral position; this point, however, is of little real importance, and should never be allowed to outweigh the distress caused by the former position to a weak and toxic patient. In severe cases the preparation of the bowel, which is at the best an exhausting process, should be abandoned altogether, for in such cases the sphincteric action may be so weak that the irrigation has to be performed while the patient is suitably padded or is placed on a bed-pan. It is best to elevate the foot of the bed slightly. The rectal tube is well greased with vaselin, the apparatus filled with fluid, and the tubing constricted while the tube is gently inserted for a distance of about 3 in.; further introduction of the tube only results in excoriation of the inflamed mucosa, kinking of the tube, stimulation of peristalsis, or, possibly, perforation; the so-called "high" rectal tube is worse than useless. The funnel is held so that the fluid level is about 1 ft. above the anus, the tubing is then released and the rate of flow carefully regulated; the correct rate is 1 in. of fluid per minute, and this can easily be adjusted by raising or lowering the funnel for a distance of about 2 ft. The tube itself should be held in the rectum throughout the operation, for if this is not done it may be extruded. Lateral pressure on the buttocks aids the retention of the injection, especially when the patient himself feels that he has taken all he can manage. The patient should be encouraged to put up with the discomfort and retain the injection as long as he possibly can. Where appendicostomy has been performed, the irrigation may be carried out through a catheter, size No. 10, introduced via the appendix. The patient should be placed upon a bed-pan and cautioned to contract the anal sphincter as little as possible, so as to permit the injection to flow through the large intestine as freely as is possible. The injection is best given on alternate days.

The following substances are used for irrigating the bowel:—

Drug	Vehicle	Approximate strength
Sodium chloride	Water	Drug dr. 4 to pt. 1 ($\frac{1}{20}$).
Sea-water	—	Vehicle pt. 1.
Sodium bicarbonate	Normal saline. . . .	dr. 4 ,, pt. 1 ($\frac{1}{20}$).
Eusol	" "	oz. 5 ,, pt. 1 ($\frac{1}{2}$).
¹ Protargol or albargin (argentum proteinate, B.P.)	" "	dr. 2 ,, pt. 1 ($\frac{1}{80}$).
Copper sulphate	" "	dr. 1 ,, pt. 1 ($\frac{1}{100}$).
Silver nitrate	Distilled water	dr. 1½ ,, pt. 1 ($\frac{1}{100}$).
Yatren.	" "	gram. 5 ,, oz. 8 ($2\frac{1}{2}\%$).

Surgical treatment of chronic bacillary dysentery.—When less heroic methods fail, and the patient's condition is slowly but pro-

¹ Not recommended. Silver protein salts are very expensive and are only soluble in cold water.

gressively deteriorating, right inguinal colostomy offers a reasonable chance of success. If so serious an operation is declined, *appendicostomy* may be urged. The cæcum and colon may now be washed out with normal saline, or with an astringent solution, through the appendix, as frequently as desired. For this purpose a No. 8 rubber catheter with a copper stylet is employed, and a rectal tube with an outflow tube. The patient should lie on his back; should the cæcum get distended and the fluid fail to pass freely, turning him slightly to the left will restore the flow.

Cæcostomy.—In cases with a polypoid condition of the mucous membrane and incessant distressing blood-stained diarrhoea, this operation should certainly be given a trial. The results have recently been eminently successful in cases which were incurable by any medicinal means (A. L. Gregg). A Paul's tube is inserted into the cæcum and the fæces are allowed to escape through it, thereby placing the whole of the large intestine at rest. The lower bowel may be washed out daily with boric-acid solution, and the wound may be closed at some subsequent period, after the large bowel has been permitted to rest for three months or more, and recovery of the mucous membrane has been observed to take place by sigmoidoscopic examination. A colotomy bag is fitted. The patient may be sent to convalesce in the country and encouraged to consume plenty of fresh eggs, milk, fruit, etc.

Yatren.—The substance known as yatren, given as a rectal injection in the strength of 1-2½ per cent. and preceded by an enema of 2-per-cent. sodium bicarbonate (1 pint), in the same manner as in amœbic dysentery (see p. 417), is found to be particularly useful in clearing up a chronic bacillary dysentery and, indeed, may be used to wash out the bowel from above downwards through the cæcostomy wound after operation.

Ispaghula.—The boat-shaped seeds of *Plantago ovata* have acquired a popular reputation in the treatment of chronic dysentery in India. The seeds are either chewed, when a gelatinous substance exudes which acts as a demulcent, or the pericarp is made into a paste, which is sold as “chilka” in the bazaars of Bombay. If taken in 1-dr. doses three times daily, it has a soothing effect.

Post-dysenteric constipation.—After the subsidence of dysentery, constipation and balling of the stools is by no means uncommon. This complication is best prevented, or met, by enemata of warm water to which a little salt—a teaspoonful to the pint—has been added, or, if the bowel is very irritable, of linseed tea or of thin rice-water. An occasional dose of castor oil, half to one teaspoonful, once or twice a week or oftener, and kept up so long as the motions

are not quite healthy, is an excellent routine practice. Medicinal paraffin, or petrolax, is also recommended.

Food and clothing.—In chronic dysentery much attention should be given to clothing and food. The former should be woollen and warm. Dysenterics ought never to feel cold. Cold bathing is very dangerous for them ; so are alcoholic drinks of all sorts. Food should be simple in the extreme. Beef, mutton, cheese, bread, coarse fruit or coarse vegetables, nuts, pickles, and the like, are, as a rule, not well borne. Fruit and fine, well-cooked vegetables in moderation are necessary and often beneficial. In obstinate chronic dysentery it is often a good thing to change the diet from slops to solids, from a meagre to a more liberal one.

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

In order to prevent the spread of bacillary dysentery in closely crowded communities, it is important to recognize, as early as is possible, all carriers of the infection and mild cases of the disease, which might otherwise escape recognition. Cunningham and others have pointed out that in the prevention of the spread of bacillary dysentery in jails, it is most essential that the stools of the inmates should be inspected macroscopically daily. Any inmate found passing blood and mucus in even slight quantities should be regarded as potentially infectious and as possibly constituting a carrier of the disease.

Prophylactic inoculations.—Graeme Gibson introduced a system of inoculation by which the toxic effects of the bacillus are neutralized by the addition of a potent anti-Shiga serum, resulting in an almost complete absence of reaction. The vaccine and serum are put up in twin phials, the bacillary emulsion being contained in one arm, the serum in the other. The first dose is 0·25 c.c., containing 500 million Shiga organisms mixed with 0·1 c.c. of serum ; the second dose, given 10 days later, contains 1,000 million organisms with 0·2 c.c. of serum.

CHAPTER XXIV

THE DYSENTERIES (*Concluded*)

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis is a term employed to indicate an infection with a protozoon—*Entamœba histolytica*. When the activities of the parasite are confined solely to the intestinal canal it produces *amœbic dysentery*, a disease insidious in its onset, chronic in its course, and with a marked tendency to relapse.

Geographical distribution.—Amœbiasis probably occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been reported from northern Europe and even from Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, and widespread in the southern United States, South America, and the West Indies.

Epidemiology.—Amœbiasis arises sporadically without any particular seasonal prevalence, and is not known to occur in epidemic form. Although the most usual method by which it spreads from man to man cannot be said to have been definitely proved, yet there is evidence that, as in the case of bacillary dysentery, houseflies play a considerable part in its dissemination. The work of Wenyon and O'Connor has shown that not only can the cysts of *E. histolytica* be demonstrated in the fæces of wild flies, but that they continue to be passed by experimentally-infected insects for sixteen hours or longer. There is also evidence to show that contaminated water and fresh vegetables, such as lettuces, may constitute suitable vehicles of infection.

Considering the susceptibility of the cysts to desiccation, it is probable that dust and sand play no part in the dissemination of this disease.

Etiology.—The discovery of amœbæ in dysentery stools was made by Lösch in 1873, and since then the intestinal amœbæ have been the object of much study. They were originally regarded as

a single organism, *Amœba coli*, but it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct amœbæ occur in the intestinal canal of man, one of which, *Entamœba histolytica*, is pathogenic, while others—*Entamœba coli*, *Endolimax nana*, *Iodamœba bütschlii*, and *Dientamœba fragilis*—are harmless saprophytic species. *E. histolytica* has been successfully cultured on egg-medium by Boeck and Drbohlav (p. 865).

Detection of entamœbæ in stools.—When present in stools, the entamœbæ (Fig. 75) are generally easy to find. All the preparation necessary is to

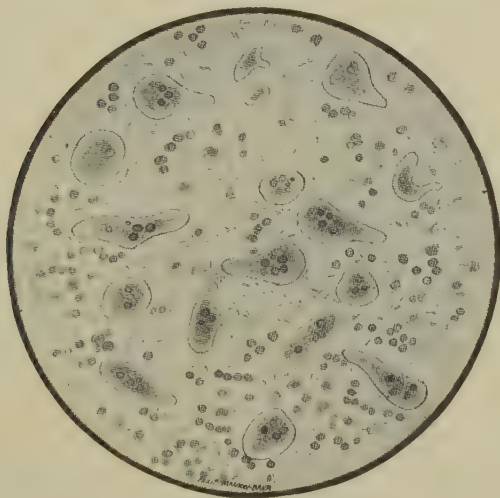


Fig. 75.—Forms assumed by active *E. histolytica* in stools, and characteristic cellular exudate. $\times 400$.

pick out a small fragment of stool shortly after being passed, and then to lay this on the slide and compress it sufficiently under the cover-glass to form a fairly transparent film. Care should be taken that the receptacle in which the stool is collected for examination is free from all traces of antiseptics. The amœbæ live only for a few hours after being passed, and are readily distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. In its vegetative phase it is recognizable by its movements, which closely resemble those of the ordinary freshwater amœba, as well as by the presence in its interior of extraneous bodies, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be detected in an excentric position. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between this amœba and the non-pathogenic *E. coli*.

In stained preparations¹ the body of the amœba is seen to be made up of two zones—a granular endoplasm surrounded by a clear protoplasmic zone or ectoplasm. The nucleus shows a characteristic uniform structure if the specimen is fresh and fixed while alive; aberrant forms with fragmented karyosomes, etc., are due to degenerative changes. (See p. 674.)

These amœbæ flow, rather than move, across the slide, and in the living state exhibit sometimes no very conspicuous differentiation between ectoplasm and endoplasm. They quickly die and degenerate when outside the body. Kept at a lower temperature for some time, they remain stationary; when the slide is warmed, they eject from time to time hyaline “blade-like” pseudopodia. Degenerate entamœbæ often contain vacuoles, but such are not present in healthy specimens. When conditions are adverse, they encyst, but before doing so undergo a reduction in size with formation of so-called precystic individuals.

Cysts.—Cysts vary much in size, and, according to Dobell and Jepps, *E. histolytica* is a species which is divisible, from the size of the cysts, into five distinct races. The smallest race produce cysts 7–9 μ in diameter; the largest, 15 μ . At present there is no adequate evidence to show that these different races differ in pathogenicity. In their substance they contain highly refractile masses composed of chromatin, generally known as chromatoid bodies, which may assume the form of blocks with rounded ends, and also a glycogen-containing vacuole. When first formed, the cyst contains but one nucleus, which measures about one-third of its diameter; this multiplies by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In its general characters the cyst nucleus resembles that of the vegetative stage.

The cysts of *E. histolytica* can survive outside the body of man for about ten days if kept moist and cool. Desiccation kills them immediately, and they survive at a low much longer than at a higher temperature. The cysts will develop and exist under suitable conditions *in vitro* in Drbohlav's medium.

Summary of life-history of Entamœba histolytica.—The active vegetative entamœbæ live on the tissues of the gut-wall, where they ingest blood-corpuscles and multiply by division. In the earliest amœbic lesions the amœbæ make their way into the follicles of the large intestine where they multiply, and partly by pressure, partly by the secretion of a cytolsin, make their way into the interglandular tissue and produce a small amœbic abscess of the mucosa. In time this abscess bursts and becomes an ulcer. A certain proportion of amœbæ leave the ulcers they produce, enter the lumen of the bowel, encyst, and pass out with the fæces. The precystic individuals, free from protoplasmic inclusions, are smaller than the ordinary forms which continue to multiply in the tissues. The typical cysts, smaller than the precystic forms, are quadri-nucleate when mature. When swallowed by another human host

¹ For the staining of amœbæ in liquid preparations, see Schaudinn's method. Appendix, p. 882. The details of amœbæ are distorted if attempts are made to dry the specimen as one would a blood-film.

they pass into the small intestine, where they hatch into amœbulæ which, in turn, attack and invade the tissues and recommence the cycle.

A characteristic feature of amœbic infection of the intestine is the periodic variation in intensity of infection which may either be connected with resistance on the part of the tissues of the host, or possibly may be a feature in the development of the parasite.

Occasionally, however, the vegetative amœbæ may migrate from their site of election in the bowel-wall, and as tissue-invading forms¹ enter the venous system and be transported to the liver, exceptionally the spleen, brain, or lung; but by so doing they become unable to complete the cycle of development as observed outside the human body. Amœbic infection of the skin around the sinus of a discharging liver abscess has been reported.

E. histolytica passers.²—The healthy passer (or excretor) of *E. histolytica* is an individual who has not suffered and is not suffering from dysenteric symptoms, but passes *histolytica* cysts, though otherwise in perfect health. Such cyst-passers may have active entamœbæ living in their tissues.

The cyst-passers may now be divided into two classes—(1) the *contact* who has never suffered from amœbic dysentery, and (2) the *convalescent* who has recovered from such an attack. It is now known that, for every abnormal person who is suffering from amœbic dysentery with the passage of vegetative forms which are non-infective to others, there are large numbers of healthy persons who continue to pass *E. histolytica* cysts, and thus constitute a perennial source of infection. The vegetative entamœba must, in either case, live at the expense of the tissues of the host. We know from the post-mortem findings in the Philippines and elsewhere that extensive bowel ulceration can occur without visible symptoms of dysentery having been present during life, and it is a matter of common experience that liver abscess may occur under these circumstances. The lesions of the mucosa may even be of microscopic proportions; the probability being that only a small percentage of those infected actually show clinical evidences of amœbic dysentery. The experiments of Walker and Sellards upon man showed that out of 20 men fed with *E. histolytica* 18 became parasitized, but only 4 developed dysenteric symptoms, though the remainder continued to pass typical cysts in their stools.

¹ Precystic individuals and cysts are found in the intestinal contents only, never in metastatic abscesses or other parts of the body.

² "Cyst-passer" is here used in the place of "carrier," a term which is not applicable to the life-history of *E. histolytica*.

By intrarectal and intracæcal injection of fæces containing cysts into cats and puppies, ulceration of the bowel-wall and even hepatic abscesses have been produced; but, although the fæces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these animals. Similar lesions can be produced in kittens by intrarectal injection of artificial cultures of *E. histolytica*.

The infection in passers of *E. histolytica* is remarkably persistent, and in all probability, unless anti-amœbic treatment is instituted, these persons continue to pass cysts for the remainder of their lives.

Incidence of cyst-passers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6·5 as against 4·5 per cent.). The carrier rate among native Egyptians, as might be surmised, was found to be considerably higher, that is, 13·5 per cent. Perhaps the most surprising outcome of the systematic examination of fæces by protozoologists during the War is evidence of the almost universal existence of the histolytica carrier. Yorke, Matthews, and Malins Smith have found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the navy in England. The two former investigators record a figure of 5 per cent., the latter one as high as 19 per cent.; and Kuenen has recorded a considerable number of indigenous infections with this parasite in Holland. In the United States the carrier-rate amongst schoolchildren is as high as 10·8 per cent. The exact significance of these figures is difficult to determine; they certainly do not mean that this comparatively large number of soldiers were suffering from gross ulceration of the bowel, for we know that indigenous amœbic dysentery was almost unknown among these troops at the time. Even among the insane, with a comparatively high cyst-passer percentage, true amœbic dysentery is very rare.

Pathology.—The earliest lesions of amœbic dysentery consist of minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growing in size and breaking down they form flask-shaped ulcers, the bases of which lie in the submucosa. (Plate XVIII, Fig. 1, facing p. 382.) These ulcers are scattered throughout the large intestine, and rarely extend above the ileo-cæcal valve.¹ The appendix may be involved. Amœbic ulceration of the ileum has rarely been reported.

The ulcers may not be larger than a pin's head or may enlarge to an inch or more in diameter, and, as the disease progresses, may become even larger. In this case the margins are rolled, the edges undermined, and the base is generally formed by the fibres of the

¹ The reported discovery of *E. histolytica* in the duodenal juice and bile-passages requires confirmation (Boyers).

muscular coat (sea-anemone ulcers). The ulcers themselves are usually capped by yellowish, greenish, or even black sloughs (Dyak hair sloughs), which may be of considerable thickness and may project into the lumen of the bowel. The lesions, as a rule, begin in the cæcum, and are scattered throughout the transverse and sigmoid colons and the rectal canal, though the intervening mucous membrane remains healthy. As a general rule, amœbic lesions extend throughout the large intestine as far down as the internal sphincter. When the process is a chronic one there is a considerable inflammation and compensatory hypertrophy of the bowel-wall. Often there may be sacculations and constrictions due to the cicatricial contractions of one part of the intestine and attenuation of another.

Thrombosis of the blood-vessels occurs at the bases of the ulcers, and often, by a process of erosion, an arteriole may be opened, and severe or fatal hæmorrhage result. Perforation by ulcers and even massive gangrene of the gut may occur, especially in the neighbourhood of the cæcum, and lead to fatal peritonitis.

In the healed or healing gut, cicatricial pigmented scars mark the sites of the ulcers. Adhesions may form between proximal coils of intestine; these may be matted together or adherent to the liver and spleen. The intestines themselves are very friable and tear readily when handled.

In chronic cases, polypoid and, it may be, gangrenous tags hang into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic fæcal matter possessing a characteristic penetrating odour.

Carcinoma has been observed to originate at the site of chronic unhealed amœbic lesions.

The cadaver shows no signs of toxic absorption, such as occurs in the bacillary disease. Apart from wasting, the other viscera exhibit few, if any, changes.

Histology.—It is thought that the amœbæ work their way down the crypts of Lieberkühn, multiply, and, by means of a cytolsin, disintegrate the tissues of the submucosa and produce a gelatinous necrosis, with little surrounding tissue reaction. (Fig. 76.) In more advanced lesions the entamœbæ may be seen lying between the muscular bundles and within the lumina of the peritoneal veins, whence they may be swept as emboli into the portal vein, and lodge in the liver, so becoming the starting-point either of an amœbic hepatitis or of a liver abscess.

The superficial layers of the slough become secondarily invaded by bacteria, though the adjacent mucous membrane is comparatively healthy and shows few microscopic changes.

Symptoms.—The *incubation period*¹ of amœbic dysentery in man, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, is estimated to be of considerable length. The fact that amœbic cysts are found in the fæces of individuals who may never have had “dysentery” in the ordinary accepted sense, apparently suggests that the disease



Fig. 76.—Section through base of amœbic ulcer, showing *E. histolytica* in the tissues. (C. M. Wenyon.)

depends upon some secondary condition, the supervention of which is the ultimate determining factor of the explosion of the active disease.

¹ The course of experimentally-produced amœbic dysentery in kittens differs essentially from the disease as seen in man. When introduced into the rectum of the cat the entamœba produces within a period of two to three days the most acute inflammation of that part of the intestinal canal to which it has gained access. The lesions differ essentially in their generalized and acute character from those observed in man, and death takes place from a secondary terminal bacterial invasion. Cysts are never formed, and chronic ulceration does not occur.

The great majority of cases of amœbic dysentery run a chronic course, with frequent intermissions and relapses. In fact, the capacity for latency is one of the most striking and characteristic features of amœbic dysentery. The *onset* is generally insidious, and the patient may complain more of diarrhœa than of dysenteric symptoms. This cannot be too much emphasized. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in a patient who, judged by clinical data, was not considered to be suffering from dysentery at all. In mild cases of amœbic dysentery the patient generally complains of sudden attacks of diarrhœa; these cases may best be described as examples of "*amœbic diarrhœa*."

The symptoms, both subjective and objective, are very similar to those described for bacillary dysentery; but as a rule the abdominal tenderness is much less acute, and has a definite distribution over the cœcum, where it may simulate appendicitis, and over the transverse colon, where it may resemble gastric ulceration. More frequently it is limited to the sigmoid colon. Should ulceration occur in the rectum, tenesmus and straining may be noted. The stools are larger than those of bacillary dysentery. They may not number more than three or four in the twenty-four hours, and they seldom exceed twelve. As a rule, they contain much dark and altered blood, which imparts a penetrating and fœtid odour; in consistence and appearance they have been compared to *anchovy sauce*. When mucus is passed, it is streaked with blood and occurs as flecks scattered throughout the fœcal mass. Occasionally, however, the motions may be formed, and only streaked with blood and mucus. Gangrenous sloughs may be passed, and even gangrene of the gut has been recorded. Unless the case is complicated by hepatitis, when the liver is painful and definitely enlarged, there is seldom any fever, nor are there any toxic manifestations. The patient, as a rule, becomes progressively emaciated, but some subjects remain in remarkably good condition although suffering from repeated relapses. The tongue is moist and coated, vomiting may occur, and generally there is complete loss of appetite. Dysuria is not a prominent symptom.

As a general rule, in uncomplicated amœbic dysentery there is no pyrexia; irregular fever sometimes observed is due to septic absorption from the bowel. Cases with periodic rigors, suggestive of malaria, are occasionally met with and may be recognized by their amenability to emetine treatment and by the discovery of amœbic cysts in the fœces. In association with amœbic dysentery there is usually a moderate leucocytosis.

The study of the clinical manifestations of amœbic dysentery

is an extensive subject and there still remain a number of obscure conditions about which some mention must be made. Intestinal amœbiasis is not always associated with dysentery or diarrhœa; it may occasionally be marked by obstinate constipation and by the association of intestinal pains or disturbances, very often with neurasthenia, with bodily and mental lassitude, furred tongue, and disordered digestion. In these cases the discovery of amœbic cysts in the fæces followed by appropriate treatment may greatly improve the clinical condition. Pathological changes in the bowel as a result of amœbic infection may lead to partial constriction of the bowel, to sacculaton, and even to gross dilatation of the colon. Very often the cæcum is specially affected and may become grossly distended with gas, and the seat of much discomfort to the patient.

Often, without treatment, the condition may subside, and the patient may be apparently cured, only to relapse after an interval of weeks, months, or it may be of years. More often the patient continues to pass loose, semi-formed stools, attacks of diarrhœa alternating with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection; it may come on while the symptoms are acute, or during a remission. The patient usually complains of great pain over the hepatic area, together with symptoms of toxæmia and considerable pyrexia. The liver itself is actually enlarged; the lower border may project below the costal margin, and be extremely tender. A pain referred to the right shoulder is also frequently present. Usually there is a considerable leucocytosis. Such a condition may subside without any active treatment. There is a good deal of evidence that in these cases the amœbæ lie actually within the liver substance, which they reach via the peritoneal vessels, but fortunately this condition is readily amenable to emetine treatment (*see* p. 413).

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

Perforation of the gut may be sudden, or preceded by intense local pain, which, if confined to the right iliac fossa, may be mistaken for appendicitis. The most frequent complication of amœbic dysentery is liver abscess.

Amœbiasis may be superimposed upon an attack of bacillary dysentery. In Egypt intestinal amœbiasis is often found in association with *Schistosoma mansoni*. Visceroptosis, great distension and sacculaton of the gut, leading to intractable intestinal

stasis, constitute some of the most distressing sequelæ of amœbic dysentery.

Diagnosis.—Generally it is safe to regard an acutely developing tropical diarrhœa as being of bacillary or amœbic origin. The clinical distinctions are unreliable; possibly some assistance may be obtained from the more rapid onset, the febrile condition, and the rapid pulse in the bacillary disease. As a rule the number of stools in bacillary dysentery is greater and their bulk less. The character of the stools should be taken into consideration. Usually they contain more dark blood, and, occasionally, they may be tarry like melæna, suggesting almost duodenal ulceration.

In these circumstances laboratory diagnosis should be had recourse to, the clinician having regard to the experience of the observer and his ability to determine whether any amœba-like body discovered in the fæces be *E. histolytica*, *E. coli*, or merely a large tissue cell, especially a macrophage (Plate XX). With practice this becomes comparatively easy. Entamœbæ may be absent in some portions of a stool though numerous in others. Several preparations must be searched with the $\frac{1}{8}$ -in. lens, and, whenever possible, a portion of mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing much blood, and it is important that the specimen should be as fresh as possible. This discovery of an active amœba containing ingested red blood-corpuscles is generally sufficient to clinch a diagnosis of *E. histolytica*. In the more chronic and latent forms of the disease the characteristic cysts must be searched for. No examination should be considered as completely excluding an amœbic infection until the stool has been searched on *each of seven* consecutive days. The cultural method greatly assists diagnosis in scanty infections.

In cases in which there is any doubt as to the identity of the cysts, staining, by the rapid or by the more prolonged iron-hæmatoxylin method, may be resorted to (p. 882). Much valuable information can be obtained by mixing the fresh fæces with a solution of Weigert's iodine (p. 881), which brings out their nuclei and other characteristics.

Thomson and Robertson are of the opinion that Charcot-Leyden crystals are encountered solely in the fæces in amœbic dysentery, and they regard their presence in this situation as being of considerable diagnostic importance (*see* Fig. 77). These crystals vary very much in size, averaging 5–25 μ ; their typical shape resembles that of a whetstone, and they are soluble in warm water, strong

mineral acids, and alcohol. They may also be found in scrapings of the bowel-wall obtained through the sigmoidoscope.

An additional feature which may serve as a means of differentiation from bacillary dysentery in the moderate leucocytosis of 10,000–12,000 which usually accompanies intestinal amœbiasis.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that a sigmoidoscopic examination, which should be conducted without an anæsthetic, may afford valuable information. As

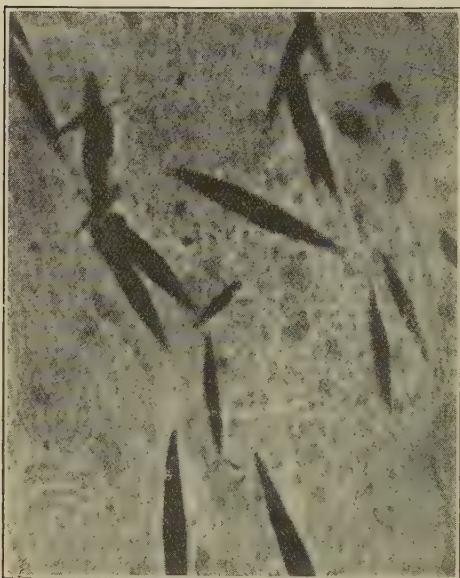


Fig. 77.—Charcot-Leyden crystals in amœbic dysentery, from scraping of amœbic ulcer; stained by Heidenhain's hæmatoxylin. $\times 1,200$. (Dr. J. Gordon Thomson.)

a general rule, small yellow ulcers with surrounding hyperæmia are seen; when scraped and examined microscopically it is often possible to find living entamœbæ in the scrapings, even when these organisms cannot be demonstrated in the patient's fæces. As compared with similar examinations in the chronic bacillary disease, the most striking fact is the absence of pain. Amœbic ulcerations may be touched and scraped without causing any sensation to the patient, while the passage of the instrument causes at the most a feeling of discomfort. The mucous membrane surrounding individual lesions shows a total absence of inflammation, and preserves its normal pinkish colour, but is usually more reticulated and folded than in a normal subject. Amœbic lesions are then seen in the crypts between the folds; early lesions may appear either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins. (Plate XXII.) Often, again, the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which the entamœbæ may be discovered in scrapings obtained by means of a probe passed through the sigmoidoscope.

In chronic, partially healed latent amœbic dysentery, or even in symptomless cyst-passers, amœbic lesions may be distinguished as minute oval or circular pits or depressions on the mucous surface. They may be almost microscopic in size, requiring a magnifying eye-piece for their detection.

X-rays in diagnosis.—Vallerino has described filling-defects in cæcum and ascending colon with deficient haustration of the bowel, which are indicative of amœbic lesions subsequent to a barium meal, but not so easily observed after an opaque enema.

Treatment.—The treatment of amœbic dysentery requires careful supervision. Specific drugs may be preceded by a purge—castor oil is the most appropriate; opium, as a routine measure, should be avoided. The dietary should be carefully regulated and in the acute stages careful nursing is important.

*Ipecacuanha.*¹—It had long been recognized in India and in the East that ipecacuanha root was a valuable drug in chronic dysentery; this was Manson's opinion based upon a wide experience in China. Its use is now a matter of history, though it may sometimes be employed. Food should be interdicted for three hours, and then 10 to 20 drops of laudanum given in a tablespoonful of water, and at the same time a mustard plaster applied to the epigastrium to counteract the emetic effects of the drug; about twenty minutes later, when the patient is under the influence of the laudanum, 20 to 30, and even as much as 60 gr. of ipecacuanha, in pill, bolus, capsule, or suspension in half-a-wineglassful of water, are administered. The dose of ipecacuanha must be continued daily for at least a week.

Emetine.—Ipecacuanha has been largely superseded by its alkaloid, *emetine*, as advocated first by Rogers. There are four alkaloids of ipecacuanha—emetine, cephæline, psychotrine, and emetamine—whose exact constitution is not yet known; but only the first-named has definite therapeutic properties.

The rationale of the action of the ipecacuanha alkaloids on *E. histolytica* cannot yet be regarded as settled.

Sellards and Leiva (1923) controvert the idea that emetine produces a secondary change in the tissues or in the serum which reacts upon the entamœba; from observations on entamœbæ in the bowels of the kitten they believe its action to be direct upon these organisms.

There is no evidence that emetine is of any value in dysenteric conditions and diarrhœa due to other causes, and therefore it should not be given indiscriminately. In excessive doses, more

¹ Brazilian ipecacuanha root (*Cephælis ipecacuanhæ*) is said to be more efficacious than the preparation from New Grenada (*Uragoya granatensis*), as it contains more emetine.

than 1 grain a day, emetine produces toxic symptoms. It may lead to asthenia, cardiac irregularity, emaciation, mental depression, and in rare cases to a neuritis which may affect a particular group of muscles and produce partial paralysis. Another curious toxic symptom is the production of diarrhoea which may possibly be considered to be due to the dysentery itself. Emetine therapy is frequently followed by a fine branny desquamation of the skin and an atrophic condition of the nails (Fig. 78). Emetine given in enema form (1-1,000) in doses of 2-3 gr., thereby directly introduced into the bowel, is not generally followed by good results. It is extremely painful and may actually provoke an acute relapse



Fig. 78.—Effects of emetine treatment on nails, showing striation and atrophy. This condition is often accompanied by increase of the lunule. (Dr. T. Jackson.)

of amoebic dysentery. No adequate explanation of this curious action has been forthcoming.

It is advisable to begin the emetine treatment with a course of hypodermic, or intramuscular, injections of emetine hydrochloride (1 gr. in 1 c.c. of distilled water) daily for ten or twelve days. This alone does not suffice for the thorough eradication of the infection from the bowel; it should be supplemented by the *double iodide of emetine and bismuth* (emetine-bismuth-iodide), containing 26 per cent. of the emetine alkaloid. Emetine is a much more effective amoebicide in metastatic amoebic lesions than it is for true amoebic dysentery.

Emetine-bismuth-iodide.—This drug is useful, especially in chronic cases and in persistent passers of *E. histolytica* cysts, and should be given by the mouth. Generally known as E.B.I., it is an insoluble powder, from which the emetine is set free by contact with the intestinal juices. Experience has shown that it passes through the intestinal canal unabsorbed if compressed into a hard tablet, or if coated with an insoluble substance, such as paraffin, vaselin, resin, keratin, or stearin. It is best made up in powder form in hard gelatin capsules, or mixed with jam or syrup. The maximum individual dose for an adult is 3 gr. per diem; it should be given for ten or twelve consecutive days. With delicate individuals and with women one should begin with a smaller dose—1 gr.—and gradually increase till 3 gr. is reached.

The drug is sold as a red powder made by Burroughs Wellcome & Co.; the capsules of gelatin are manufactured by Parke, Davis & Co. No. 4 size capsule will contain 1 gr. of E.B.I., while 3 gr. can be accommodated within No. 1 size. If the full dose is given, it is better from the point of view of the patient to take one capsule containing 3 gr. each. When treatment is commenced with smaller doses the patient becomes gradually accommodated to the drug.

It is important to observe certain precautions in giving the drug. When given at 10 p.m., the last food should be taken at 6 p.m., and nothing, not even a glass of milk, taken after. The patient should remain absolutely at rest, he should endeavour to go to sleep, and any saliva should be wiped from the mouth and not allowed to be swallowed.

The practitioner should remember that vomiting and diarrhœa are to be expected in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. Vomiting, unless excessive, is not to be regarded as a contraindication; if no symptoms of nausea supervene, it is possible that the cachets are not being dissolved and their contents set free. It is necessary that the patient should remain in bed and partake of a liquid or milk diet with one egg and toast.

Excessive vomiting and nausea may be prevented by 10–15 min. of tinct. opii given half-an-hour previously, or, in some patients, by luminal, $1\frac{1}{2}$ gr. Most patients lose about 5 lb. in weight while under treatment. The condition of the heart and pulse should be noted daily, but the treatment should not be discontinued unless depression becomes severe. Alcohol in any form should be prohibited. When the cure is completed the patient should be gradually permitted to resume an active existence, but dieting (see p. 419) is still necessary.

For a *relapsing case*, more than one course of treatment with E.B.I. may be necessary. It is now considered advisable, after the first twelve-day course, to examine the stools frequently for *E. histolytica* cysts. Several separate examinations are necessary before a patient may be pronounced free from infection; the first one should be carried out in the first week after treatment, and subsequently on several occasions during the next three months. The results of treatment are still better controlled by periodic sigmoidoscopic examinations; for some considerable time after the disappearance of the more active lesions, small pits or depressions in the mucous membrane may still be seen.

The results obtained by E.B.I. treatment are as a rule more permanent than those obtained by emetine alone, but, unfortunately, in a small proportion of cases the entamœbæ, known as emetine-resisting forms, recur in spite of treatment. Speaking generally, the cases remain outwardly well for a period of six to eight weeks after cessation of treatment, and then a relapse sets in. Intravenous injections of neosalvarsan appear to have a beneficial influence, probably owing to their tonic effect. Those with a syphilitic history especially are greatly benefited, and sometimes completely cured, by the adoption of antisyphilitic measures concurrently with the administration of E.B.I. It is therefore advisable to try the effect of potassium iodide in what appear to be incurable cases of amœbic dysentery. In the Editor's experience the more acute the onset, the more advanced the disease appears to be, the more rapid and permanent are the results of E.B.I. treatment.

A modification of emetine-bismuth-iodide known as emetine periodide (E.P.I.) has been produced by Martindale, and appears to be much less toxic. It is given in capsules in the dose of 6 gr. daily, combined with tablets of ox-bile (which is said to increase the liberation of emetine) in doses of 5 gr. three times a day. Vomiting and other toxic phenomena frequently associated with E.B.I. are usually not seen after the administration of E.P.I. Some diarrhœa is produced, but recent experience shows that E.P.I. is not nearly so efficacious in curing chronic cases as is E.B.I.

Auremetine (Willmore and Martindale), a compound of auramine (an aniline dye) with emetine. It is given by the mouth in the form of a dark-maroon powder which is insoluble in water. The dose is 1 gr. given in soft gelatin capsules four times daily after food, on alternate days for seven days, and then daily till a total of 40-60 gr. is ingested as a course. It is said to give rise to no nausea or

vomiting, but it is not clear whether the results obtained are superior to those of E.B.I.

As an adjuvant to emetine treatment, tablets of "kurchee" bark (which contains an alkaloid—conessine), in 10-gr. doses three times a day, apparently stave off a relapse in some intractable cases.

Stovarsol,¹ 4 gr. twice daily for a course of a week at a time, appears to act beneficially in checking the diarrhoea in chronic cases, but there is no evidence that it has a lethal effect on the entamœbæ. The exhibition of stovarsol must be carefully watched as toxic erythema or even an arsenical exfoliative dermatitis may ensue.

Yatren treatment.—Yatren No. 105² is an iodine-oxyquinolin-sulphonic-acid combination in which the iodine is firmly bound; it is considered to be an intestinal disinfectant and cell-stimulant, and has been well reported on. Yatren can be given by the mouth, by enema, subcutaneously, or intravenously. The dose is 1 grm. (15 gr.) in powder form, in capsules, or keratin-coated pills, three times a day for an adult, for ten days; after an interval of one week the course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinolin test (green colour with perchloride of iron). Yatren in pill form is considered to act best when the acute symptoms have been controlled by emetine and in conjunction with that drug.

In the Editor's opinion, in order to obtain permanent results, yatren must be given by the rectum in the form of a rectal injection as well as by the mouth. Given in this manner yatren has distinct amœbicidal action. The bowel must first be washed out and cleared of mucus by means of an enema (1 pint) of 2-per-cent. sodium bicarbonate. This is best given at 8 a.m. One hour later 200 c.c. (8 oz.) of a 2·5-per-cent. solution of yatren in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain the solution as long as possible, which he is usually able to do for 8–10 hours. The solution is then excreted per rectum as a greenish liquid containing mucus and débris derived from the bowel. The course of injections is continued when well tolerated, for ten days. Sometimes a longer period may be necessary, or even the course may be repeated two or three times with a week's interval between each course. Strict dieting and rest in bed are absolutely necessary.

¹ An arsenical preparation, acetyl-oxy-amino-phenyl-arsinic acid, obtainable from Messrs. May & Baker.

² To be obtained from the Beringwerke, Marburg, Germany.

In Germany and the Dutch East Indies, yatren is given sometimes in stronger doses up to 5-, or even up to 10-per-cent. solution, but in the latter strength is apt to cause some pain and diarrhoea.

Combined treatment.—The combination of yatren given by the rectal route and emetine-bismuth-iodide by the mouth, for a ten-day course, is remarkably well tolerated and appears to be more lasting and efficacious in its results than when these drugs are given singly. The E.B.I. is given as described, at night; the yatren is injected by day. This method is specially useful in chronic and resisting cases. As the treatment is continuous, day and night, the parasite is given no chance to recuperate. In the Editor's opinion this method gives the best results.

Rivanol, a derivative of acridine, injected per rectum, appears to have a somewhat similar action to yatren. A preliminary cleansing, non-irritating enema is given and rivanol in distilled water is diluted 1 : 2,000; of this 500–800 c.c. at body-temperature is given per rectum with the patient lying on his side or in the knee-elbow position. The injection must be retained as long as possible, at least fifteen minutes. A course of ten or more treatments is necessary.

Bismuth subnitrate.—As an adjuvant to emetine treatment Deeks and James strongly advocate bismuth subnitrate in heroic doses—180 gr. mechanically suspended in a tumblerful of milk or water every three hours, night and day, in severe cases. Occasional untoward effects are noted, such as cyanosis and forcible action of the heart, and they are due to impure bismuth. During the first ten days of this treatment a strict dietary is necessary; thereafter a non-irritating diet must be persisted in for two or three months.

Treatment of hepatitis.—The possible supervention of amœbic hepatitis with pyrexia and rigors should steadily be borne in mind. During the whole course of an attack of amœbic dysentery, and for months afterwards, the condition of the liver must receive the most careful attention. We may not be able to prevent abscess of this organ; but if pain seems to suggest it, we can try by means of full and repeated doses of emetine, saline aperients, rest, low diet, fomentations, dry-cupping, and similar measures to avert a very grave complication. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the intestines; in some cases actual aspiration of the liver (hepatic phlebotomy) has a wonderful effect.

Perforation of amœbic ulcer.—In order to avoid fatal peritonitis, every effort to diagnose perforation of the large bowel should be

made directly rupture has taken place. This is usually very difficult. Two successful instances, at least, have been recorded.

Diet.—The question of a suitable diet in the convalescent treatment of amœbic dysentery is an all-important one; the precautions advocated are necessary in view of the tendency of this disease to relapse when the patient indulges in rich and highly nitrogenous food, or foods containing too much starch.¹ Alcohol, unless taken in small quantities, certainly predisposes to relapse. The following diet is advocated to be taken for six weeks after active treatment:—

Permitted.—Porridge; eggs; filleted or fried fish—haddock, plaice, cod, sole or whiting; toast or rusks; milk puddings—rice, sago, semolina, ground rice; spinach or young peas, vegetable marrow, cauliflower; plain cakes; fruit jellies; stewed pears or peaches; baked apples; bananas, grapes; tripe, brains, sweetbreads; chicken boiled in rice; rabbit; game—pheasant, partridge, pigeon.

Not permitted.—Cheese; new bread; potatoes; fats; suet puddings; rich cakes with raisins or spices; pastry of all kinds; pickles.

Beverages.—Light claret; no spirits, beer, or stout.

Meat.—No red meat for six weeks, then commence with minced lean mutton midday.

Resistant cases.—Whatever treatment is adopted, cases will be encountered from time to time in which the infection persists. This apparently is due to the strain of entamœbæ and the site of the amœbic lesions. In these cases, surgical measures, even as a last contingency, must be avoided. There is at present no evidence to show that amœbic lesions of the large intestine will yield more readily to solutions of yatren or emetine poured into the gut through a cœcostomy opening.

Prophylaxis of amœbiasis is practically the same as that already described for bacillary dysentery, and depends upon efficient sanitation, measures directed especially against the housefly, which has been proved to be a carrier of the amœbic cysts, and the avoidance in the tropics of raw vegetables or other foods that may have been contaminated by human fæces. As the cysts of *E. histolytica* can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amœbic infection is mostly water-borne. The problem of dealing with human carriers of *E. histolytica* cysts is one that is engaging the minds of sanitarians at the present time. It is not likely to arise in countries supplied with a proper system of sanitation, but in no case ought a cyst-carrier to be employed as a cook or mess orderly,

¹ This statement has some experimental basis. Brumpt has shown that in artificial culture the entamœbæ eagerly ingest starch grains (see p. 675).

or placed on water duties. Wherever possible, cyst-carriers should be treated with emetine-bismuth-iodide.

COMPLICATIONS OF AMŒBIASIS

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMŒBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds in its distribution with amœbic dysentery. While the *entamoeba* is the principal element in its production, its incidence depends probably on the effects of high atmospheric temperature and tropical habits on the European liver.

Etiology. Relation to dysentery.—There can be no question as to the existence of an intimate relationship between amœbic dysentery and liver abscess. Numerous and well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. It will be remembered that extensive amœbic ulceration may exist without exciting any subjective symptoms whatever. Moreover, many patients suffering from liver abscess forget, or fail to mention, the occurrence of a previous dysenteric attack, or may mislead the physician by describing such an attack as “diarrhoea” so that the relationship is much more intimate than even statistics would indicate. In the great majority of cases the dysentery antedates the abscess, it may be by twenty years, as in a case cited by Low.

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is rare among the natives. Thus, in the native army of India the proportion of deaths from liver abscess to the total mortality in 1894 was only 0·6 per cent., whereas in the European army it was 7·4 per cent. Man for man, the relative liability of the European soldier and the native soldier was as 95·2 to 4·8. This disproportion holds, in spite of the fact that the native is more liable to dysentery than the European.

It is well known that European women in the tropics, though quite as subject to dysentery as European men, rarely suffer from liver abscess; children hardly ever. It is most common between the ages of 20 and 40.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver; in some instances this condition may be more or less confined to one lobe or even part of a lobe. Later, as we know more especially from observations in cases that have died from the attendant dysentery, one

or more greyish, ill-defined, anæmic, circular patches, $\frac{1}{2}$ –1 in. or thereabouts in diameter, in which the lobular structure of the gland cannot be made out, are formed. These grey spots are very evident on section of the organ. A drop or two of a reddish, gummy pus may be expressed from the necrotic patches—for such they are. Still later, the centres of the patches liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by molecular breaking down; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood and subsequent breaking down of the intervening septa. The walls of such an abscess have a ragged and rotten appearance.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many abscesses. When single, the abscess sometimes attains a great size. Frequently it is as large as a coconut, or even larger; it has happened that the entire liver, with the exception of a narrow zone of hepatic tissue, has been converted into

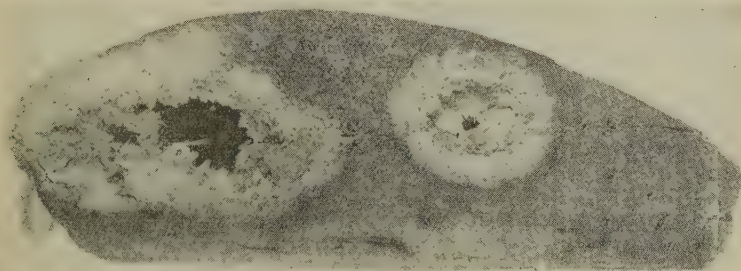


Fig. 79.—Multiple liver-abscesses from a case of acute amœbic dysentery showing characteristic structure and zone of acute hyperæmia. Quarter nat. size. (*Orig.*)

a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange. (Fig. 79.)

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left and smaller lobes. What might be termed the seat of election is the upper part of the right lobe.

Adhesions to surrounding organs are frequently, though not invariably formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually coexists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cæcum.

Pulmonary inflammation and abscess from escape of liver pus into the lungs are sometimes discovered post mortem. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac as a whole being shut off by adhesions.

Liver pus.—The naked-eye appearance of liver pus is peculiar, and almost characteristic. When newly evacuated it is usually chocolate-coloured, and streaked, or mixed, with larger or smaller clots or streaks of blood, and

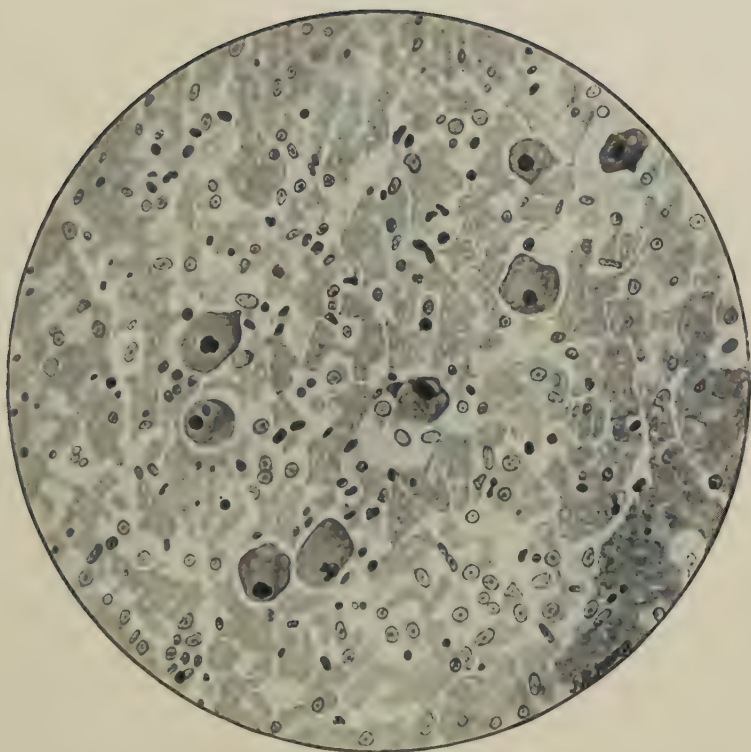
here and there with streaks of clear mucoid or yellowish material. It is so thick and viscid that it will hardly soak into the dressings; it lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and there little islands of what may be described as laudable pus may be made out in the brown mass. Sometimes it contains considerable pieces of necrotic tissue. Occasionally, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive unless the abscess lies near the colon, in which case it may have a fæcal odour. Under the microscope many blood-corpuscles are discoverable, besides much broken-down liver tissue, large granular pigmented spherical cells, leucocytes, debris, oil globules, hæmatoidin crystals and, occasionally, Charcot-Leyden crystals, and entamœbæ; rarely, the ordinary pyogenic bacteria.

Entamœbæ and pyogenic organisms.—The experience of tropical abscess in Egypt, India, and elsewhere is that entamœbæ may be detected in considerably over half the cases. Usually they cannot be found in freshly aspirated liver pus, or in the matter which escapes during operation, but they appear, often in great profusion, four or five days later in the discharge from the drainage-tube. In these circumstances they may occur in strings of eight or ten, an arrangement suggesting that they had developed in some tube such as a blood- or bile-vessel. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed. Their appearance in the pus coming from the walls of the abscess a few days after operation suggests that the habitat of the parasite is not so much the pus occupying the general abscess cavity as that immediately in contact with the wall and the breaking-down tissues themselves. (Plate XXIII.) The pus from a large proportion of cases is sterile, but occasionally one may become secondarily infected by *Bacillus coli*. Cysts of *E. histolytica* are never found. The Editor has succeeded in growing the amœbæ from liver-abscess pus on Drbohlav's medium.

Encystment.—In rare instances the pus of liver abscess, instead of possessing the chocolate colour and viscid consistence described above, is yellow and creamy. This is particularly the case when the abscess becomes encysted—an occasional event. The walls of these encysted abscesses are thick, smooth, resistant, and fibrous. In time their contents become cheesy, and ultimately cretified; in the latter event the cyst shrivels up and contracts to a small size.

Rogers considers that cirrhosis of the liver which is so frequent in India may be a sequel to liver abscess.

Symptoms.—There is a great variety in the symptoms which liver abscess may produce. As a general rule the patient is a man who has long resided in the tropics and who may have at some time or other suffered from subacute attacks of dysentery. He becomes conscious of a sense of weight and fullness in the right hypochondrium, and later he suffers from sharp stabbing pains over the hepatic area, and perhaps a dry cough which makes the pain more apparent. In a considerable proportion of cases a sensation of uneasiness or actual pain, rheumatic in character, is felt around the right shoulder-joint, especially at night-time.



Microscopical section of liver abscess, showing *Entamoeba histolytica* at margin of abscess cavity surrounded by necrotic liver cells.

LIVER ABSCESS.

PLATE XXIII

Usually the pain and tenderness are in the skin around the acromial region. It is reflex in character due to irritation of the phrenic nerve, and reflected through the fourth cervical root from which the supra-acromial and supra-clavicular cutaneous nerves arise in the cervical plexus. In left-lobe abscess the pain is referred to the *left* shoulder joint. Soon he becomes feverish, particularly towards the evening, and may experience a few short rigors. He begins to lose flesh, and his complexion assumes a curious yellow, muddy tinge. The quotidian rise of temperature now becomes a regular feature, the thermometer every evening touching 102° F., and sinking to below normal in the morning. (Chart 31.) The pyrexial bouts are accompanied by most profuse sweats necessitating the frequent changing of clothing during the night. On

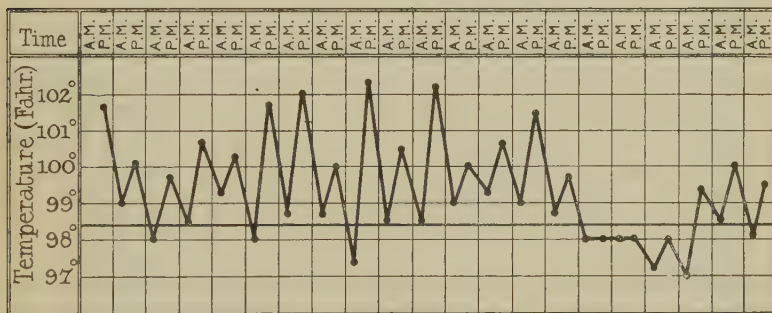


Chart 31.—Amœbic abscess of liver. (Orig.)

examination the patient is found to be emaciated, his tongue furred, the extremities cold and clammy; the breath is shallow and mainly thoracic; sometimes an actual fullness in the epigastrium may be observed; considerable discomfort, and, it may be, deep-seated pain are produced by general palpation and heavy percussion over the right hypochondrium. In the majority of cases the lower border of the liver is found to be enlarged below the costal margin; sometimes, but less frequently, it extends upwards an inch too high, while posteriorly it can be detected from an angle of the scapula to the costal margin. It may be further observed that the line of dullness is arched along its upper border, and that it is altered by changes of position; the upper line descending when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender spots may be discovered in the lower intercostal spaces; the spleen is not enlarged. On auscultation, a pleuritic rub may be detected at the base of the right

lung, or signs of compression such as inspiratory crepitations, decreased breath-sounds, and a diminution of vocal fremitus may be noted at the right base. Pain is usually relieved by lying on the affected side.

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position that of an enlarged spleen, may be present in the epi- or hypogastrium, and there is usually some involvement of the base of the left lung. The blood shows a well-marked polymorphonuclear leucocytosis of 15,000–25,000, though in some rare cases no rise of the leucocytes occurs.

As the case progresses, the patient becomes more emaciated; hectic fever with drenching nocturnal sweats continues; the liver dullness and pain may increase; or the general enlargement may somewhat subside, and percussion may reveal a local bulging, upwards or downwards. If the abscess which has now formed is not relieved by operation, after months of illness the patient may die worn out; or the abscess, which has attained enormous dimensions, may burst into the right lung or pleura, or elsewhere, and be discharged, and either recovery, or death from continued hectic fever and exhaustion or from some intercurrent complication, ensue.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver; or, perhaps, until after death, when the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent in type; rarely temperatures of 103° and 104° F. may be recorded. There is not one single cardinal sign which may not be absent in hepatic abscess; thus, large collections of pus have been noted unattended by fever of any description. Marked rigors are rare, but when present indicate threatened rupture of the abscess through the diaphragm or into some viscus. The sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes occur, while rheumatic-like pains and swellings, which may accompany any chronic specific infection, may be noted.

Pain of some description is rarely absent. A sense of fullness and weight in the region of the liver, which may be referred to the infra-scapular region, is commonly complained of; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, at the moment the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Pain in the shoulder is said to be present in about one-sixth of the cases, and may be the only symptom complained of. It may be noted before the advent of the fever.

Attention may be drawn to the respiratory symptoms; a cough of a painful character, possibly due to reflex irritation of the diaphragm, may be a prominent symptom, while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side; if the abscess is on the right, lying on the *left* side becomes distressing owing to adhesions, or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed; flatulence and diarrhoea are frequently noted. There may be concurrent dysentery.

The *area of hepatic dullness* is usually extended upwards and downwards, rarely horizontally. The upper line of dullness is not, as a rule, horizontal as in hydrothorax; usually, on approaching the spine it turns downwards.

The heart may be displaced laterally or upwards by pressure of the abscess when this is of a large size. Tachycardia and cardiac irregularities may result from toxic absorption or from pressure.

Swellings in the epi- or hypogastrium may be noted, simulating closely intra-abdominal tumours; varicosity of the epigastric veins may also be observed. Local *œdema* over one or more intercostal spaces is sometimes apparent; local *bulging* usually indicates the pointing of the abscess.

Friction rubs, pleuritic or peritoneal, may sometimes be found; while pneumonic signs at the right base indicate contiguity of the abscess to the diaphragm.

The abscess may rupture into any contiguous organ, and thereby produce spontaneous cure; most generally it ruptures into the lung or pleura—when into the *lung*, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood; generally this process is much more gradual, a few drachms being brought

up at a time, but in favourable cases the expectoration gradually diminishes. Amœbic abscess of the lung—often resulting from trans-diaphragmatic rupture—is liable to be mistaken for pulmonary tuberculosis. Amœbæ are not usually found in the expectorated pus, but on two occasions the Editor has been able to recognize striated muscular fibres from the diaphragm.

Arrest of the discharge may not mean recovery; cessation of the cough may be followed by a rise of temperature and a re-appearance of night-sweats. The alternate emptying and refilling of the abscess cavity may recur many times before recovery finally takes place. In some cases expectoration never ceases, and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers.

A sudden rupture is often accompanied by the passage of melænic stools.

The appearance of the expectorated liver-pus is usually pathognomonic, being chocolate-brown in colour and particularly viscid. When hæmorrhagic, these cases are very apt to be treated as examples of tuberculous hæmoptysis.

Rupture into the *pleura* may lead to a suddenly developed pleural effusion, which may give rise to all the signs of empyema. Aspiration above the line of the pus in these cases may yield a clear yellow and highly albuminous pleuritic fluid.

An hepatic abscess may rupture into the *stomach*, causing vomiting of pus; into the *bowel*, causing diarrhœa and discharge of pus in the fæces; or it may burst, with fatal results, into the *pericardium* or *peritoneum*.

Finally, spontaneous rupture may take place through the skin of the abdominal wall, and the abscess thus empty itself in a painless and natural manner. This is the most favourable natural cure of liver abscess. The skin itself may become secondarily infected with amœbæ.

Mortality.—Formerly the case-mortality was high, 50–80 per cent., but at the present day, owing to the use of ipecacuanha and emetine, and to recognition of the intimate connexion of liver abscess with amœbic dysentery, the adoption of improved methods for the evacuation of pus, combined with medicinal treatment, has brought the mortality-rate to practically nothing. Death, when it ensues, may be due to pressure on the abscess, to rupture and gangrene of the abscess-wall, to pneumothorax, to pneumonia, to associated dysentery or other intercurrent disease. Recovery may follow encystment or, possibly, absorption of the abscess.

Diagnosis.—Of all the grave tropical diseases, none is so frequently overlooked as abscess of the liver. Acute sthenic cases are readily enough recognized ; not so the insidious asthenic cases.

The most common mistakes in diagnosis are : (1) Failure to recognize the presence of disease of any description, even when an enormous abscess may occupy the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition so often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and vice versa—for example, hepatitis of a non-suppurative nature, such as that attending malarial attacks ; suppurative hepatitis before the formation of abscess ; syphilitic disease of the liver—softening gummata which are often attended with fever of a hectic type ; pylephlebitis ; suppurating hydatid ; gall-stone and inflammation of the gall-bladder ; subphrenic abscess due to ruptured gastric or duodenal ulcer or appendix abscess ; abscess of the abdominal or thoracic wall ; pleurisy ; encysted empyema ; pyelitis of the right kidney ; schistosomiasis ; scurvy and similar blood-diseases associated with hepatic enlargement ; ulcerative endocarditis ; kala-azar ; undulant fever ; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Frequently a correct diagnosis can be arrived at only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health ; and to suspect it in all obscure abdominal cases associated with evening rise of temperature, and this particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may mean abscess of the subjacent liver.

The presence of *Entamoeba histolytica* cysts in the fæces is suggestive, but by no means conclusive, of amœbic abscess. They are found in about 27 per cent. of cases, and amœbæ may be cultured from the fæces in cases in which they are not visible under the microscope.

An X-ray examination may confirm the upward enlargement in the liver, and bulging of the right dome of the diaphragm, which does not move on respiration ; should, however, the abscess be situated in the centre of the liver, even if it be of considerable size,

no definite information is obtainable by radiography. A blurring of the outline of the diaphragm occurs if the abscess is situated near the upper surface of the liver.

The lævulose-tolerance test, as recently introduced by Maclean, Spence, and Brett, forms a valuable indication of hepatic disease, and may afford striking confirmatory evidence in amœbiasis of the liver as well as in hepatic abscess (Covell).

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness or even rigor coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. So common is the error that Osler said he hardly ever met with a case of liver abscess which had not been drenched with quinine; and this has been the experience of others. Medical men have made this mistake not only in their patients but in their own persons. The periodicity of the fever, and the presence of a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is of no great moment, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need be looked for if diagnosis is not quite accurate.

A more serious error, however, is to overlook the presence of leucocythæmia, pernicious anæmia, or scurvy, and to proceed to aspirate an enlarged liver on the supposition that the symptoms arise from abscess.

Diagnostic aspiration.—In order to make the diagnosis of liver abscess certain, aspiration must be resorted to. When the needle enters the liver, an up-and-down pendulum-like movement will be communicated to its outer extremity, in harmony with the rising and falling of the organ in respiration. If the needle does not exhibit this movement its point may be in an abscess cavity, but such an abscess is not in the liver.

Treatment.—Hepatitis which has not proceeded to abscess-formation should be treated, especially if dysentery be present or has been antecedent, with full doses of emetine or of ipecacuanha, repeated once or twice a day for two or three days or longer, by a cautious use of the purgative sulphates, and with poultices, rest, and low diet (*see* p. 418). If there be much pain, relief may be afforded by either wet- or dry-cupping over the liver, or by leeches around the anus. Ammonium chloride, 20-gr. doses three times a day, is usually prescribed.

When the occurrence of rigor, or the development of hectic

fever, or the appearance of local bulging, or the persistency of the fever and of the local symptoms, gives ground for suspecting that abscess has formed, active medication must be suspended, a somewhat improved dietary prescribed, and measures taken without unnecessary delay to locate by means of the aspirator the position of the pus.

Preliminary aspiration.—When he uses the aspirator the surgeon must be prepared to continue till all the pus is evacuated, or under exceptional circumstances, operate.

Deep cocaine anæsthesia usually suffices, but nervous subjects should undergo general narcosis. A medium- or full-sized aspirator needle should be used, as the pus, owing to its nature, may not flow through a cannula of small bore.

If there are localizing signs, such as a tender spot, a fixed pain, a localized œdema, localized pneumonic crepitus, pleuritic or peritoneal friction, these should be taken as indicating, with some probability, the seat of the abscess and the most promising spot for exploratory puncture. If none of these localizing signs is present, then, considering the fact that the majority of liver abscesses are situated in the upper and back part of the right lobe, the needle should, in the first instance, be inserted in the anterior axillary line in the 8th or 9th interspace, about 1 or $1\frac{1}{2}$ in. from the costal margin, and well below the limit of the pleura. The instrument should be carried in a direction inwards and slightly upwards and backwards, and, if found necessary, for 3 to $3\frac{1}{3}$ in.¹ At least six punctures should be made before the attempt to find pus is abandoned. Provided there is complete absence of breath-sounds, of vocal fremitus and resonance over the lower part of the right lung, and pus has not been reached from lower down, then the pleura or lung may be disregarded, and puncture made anywhere below the line of the nipple and angle of the scapula, or wherever the physical signs suggest. Serous fluid from the pleura may be obtained by aspiration. It indicates an underlying abscess. The fluid is highly albuminous and contains a number of polymorphonuclear cells.

The surgeon should be encouraged to make early use of the aspirator by the fact that its employment, even where no pus is discovered, is not infrequently followed by rapid improvement in all the symptoms. Many such cases are on record. *Hepatic phlebotomy*, as Harley designated the removal from the liver of

¹ The peculiar brownish fluid resulting from the action on blood of the carbolic lotion that had been used to sterilize the exploring syringe has been mistaken for pus. To obviate so grave a mistake the exploring syringe should be washed out with boiled water before use.

a few ounces of blood by the aspirator needle, is a measure of proved value in hepatitis. With due care, risk from hæmorrhage is small; it is very small indeed in comparison with the risk of allowing an hepatic abscess to remain undiscovered and unopened.

Some surgeons, in order to obviate the small risk from hæmorrhage attending aspiration through the abdominal or chest-wall, prefer to expose the surface of the liver by a short incision and then explore.

Drainage by aspiration.—Rogers originally maintained that, for many reasons, open operation, especially if the pus be forcibly aspirated and combined with emetine treatment, is unnecessary. If the abscess be solitary, as the majority are, and not loculated, the pus may be evacuated by means of a Potain's aspirator. Many cases have now been treated on this plan with favourable results. The death-rate has been reduced to almost nil, the shock to the patient is negligible, and several pints of pus can be evacuated. The needle of the aspirator is directed into the abscess cavity (a preliminary exploration by means of a small syringe appears to be unnecessary), and negative pressure by means of the exhaust bottle applied. Occasionally the pus may reaccumulate, but it can easily be evacuated at a second operation. The method is so simple that it can be practised in the patient's home in the absence of facilities offered by an operation theatre. The rate of recovery is remarkably rapid, and the patient's stay in hospital is equally short.

An effusion of serum generally takes place into the abscess cavity after aspiration. The swelling and pain thus produced may give rise to symptoms simulating a reaccumulation of pus, while a passive effusion of serum into the pleural cavity immediately adjacent to the liver abscess sometimes occurs.

In cases with cardiac or pulmonary embarrassment, aspiration can be efficiently carried out under local infiltration of skin and muscles with 2-per-cent novocain, to which is added 1:1,000 adrenalin in the proportion of 10 drops to the ounce. The passage of the needle through the liver substance is painless. Should, however, the abscess point into the abdominal cavity, a general anæsthetic is advisable, for an open operation may become necessary. Occasionally the pus proves to be so viscid that complete evacuation takes an hour or more to complete; in these circumstances eusol in saline (half-strength) should be injected into the abscess cavity in order to dilute the pus.

A thorough course of emetine-bismuth-iodide and yatren should

be given as an after-treatment to operation in order thoroughly to eradicate the infection from the bowel; but when continuous drainage is necessary, Manson's method may be employed.

Manson's method.—This method of aspirating liver abscess is of considerable historic interest and is one still frequently employed. The necessary apparatus (Fig. 80) consists of a large trocar and cannula (*a*), 4 to 5 in. long by $\frac{3}{8}$ in. in diameter; a steel stilet (*b*), at least 14 in. in length; two metal buttons (*c*, *d*), $\frac{1}{4}$ in. at their greatest diameter, with long ($\frac{1}{2}$ in.), hollow, roughened necks into which the ends of the stilet fit loosely; 6 in. of $\frac{1}{2}$ -in. stout drainage-tubing (*e*). While the ends of the drainage-tubing are held

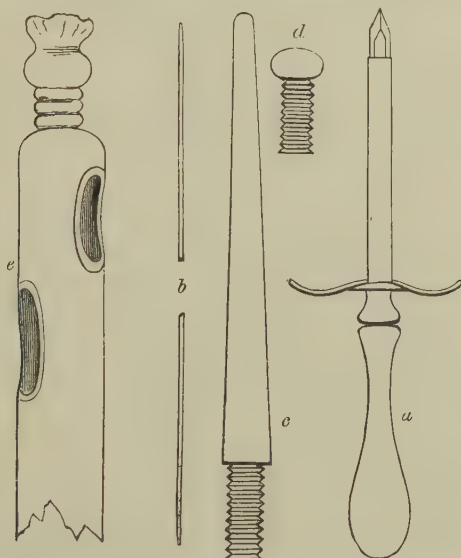


Fig. 80.—Apparatus for operation for abscess of the liver
(*a* and *b* reduced).

and well stretched by an assistant, they are firmly lashed to the stem of the buttons, over the ends of the shorter (*d*) of which, for additional security, the tubing is also tied (*e*). Two large holes, to provide for free drainage, are now cut close to one end of the drainage-tube. The tube is then mounted on the stilet by inserting one end of the latter through one of the drainage holes and lodging it in the hollow neck of the distal button (*c*), and thereafter so stretching the rubber that the other end of the stilet can be inserted into the neck of the other button (*d*). When thus stretched the drainage-tube should be capable of passing easily through the cannula. The apparatus being so prepared and rendered thoroughly aseptic by boiling, and the direction of the abscess and its depth from the surface having been carefully ascertained by means of the aspirator and noted, the aspirator is withdrawn and an incision, about 1 in. in length, made through the skin at the site of the puncture. The trocar and cannula are then thrust into the abscess and

the trocar withdrawn. After allowing a small quantity of pus to escape, so as to relieve any tension that may be present in the abscess sac, the stretched drainage-tube, fenestrated end first, is slipped into the cannula and carried to the back of the abscess. Holding the drainage-tube firmly and maintaining it carefully in contact with the back of the abscess with one hand, the surgeon withdraws the cannula with the other. The stretched drainage-tube still firmly grasped, the button on the free end of the apparatus is slipped off the stilet, the end of which is made to perforate the drainage-tube close to the button. This it readily does, and the drainage-tube is allowed slowly to resile towards the fixed end still held in contact with the back of the abscess. When the drainage-tube has completely retracted, the stilet is withdrawn. The drainage-tube is then transfixed with a safety-pin inserted close to the skin of the abdomen, and the superfluous tubing cut off.

Open operations.—The open operations for liver abscess performed in English practice will now be described. The route for opening the thoracic or abdominal wall varies according to circumstances as follows :

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left *in situ* and the abdomen is incised for a length of 3 in., the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze and the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of rib had better be resected. The diaphragm should then be stitched to the thoracic wall, or, better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumo-thorax will result, but this is not necessarily a serious contingency. On no account should pus be permitted to enter the pleural cavity.¹

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge.* If there is the slightest indication, such as rise of temperature, that pus is being retained, the drainage

¹ If pleural and peritoneal adhesions are not present, it is usually advisable to pack the cavity with gauze, and complete the operation in two days' time.



Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A = collection of pus in pleural cavity; B = valve-shaped opening through diaphragm at site of abscess in liver. (*Orig. case. Radiograph by Dr. M. Berry.*)

LIVER ABSCESS.

must be rectified and the sinus, if necessary, dilated with forceps and finger, and a full-sized drainage-tube introduced as far as it will go. If this does not suffice, a counter-opening may have to be made. *Delay in remedying imperfect drainage is a serious—it may be fatal—error.*

Should an abscess on being opened be found to be septic, or should it become so, it must be flushed out daily, or twice a day, with a weak non-mercurial antiseptic, and a counter-opening made if necessary. Continuous drainage by the Carrel-Dakin tube method and daily eusol irrigation is often very successful.

After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If it be deemed that there is another abscess, this should be sought for with the aspirator and, if found, drained.

It is advisable to give emetine in 1-gr. doses hypodermically, both before and after operation, and continue it for a fortnight, whichever operation is employed.

If any symptoms of hepatic inefficiency due to extensive destruction of liver tissue are noted, the presence of diacetic acid or a high ammonia coefficient in the urine should form an indication for the oral or rectal administration of glucose and sodium bicarbonate, or in some cases for the intravenous injection of these drugs in 5- to 10-per-cent. solution.

Treatment of abscess discharging through the lung.—In the case of abscess discharging through the lung and, although emetine has been freely administered, not progressing favourably, the question of obtaining by surgical means more efficient drainage must be considered. There are two possibilities which render interference desirable: (a) Continued discharge of pus and blood, with or without attendant hectic fever; a condition which, if it persist, will, in all probability, in the end, kill the patient. (b) Not infrequently, prolonged discharge through the lung may induce fibrotic changes in that organ, or may give rise to pneumonia, or to abscess of the lung with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XXIV.)

In all cases of abscess discharging through the lung a careful register should be kept of three things—body-temperature, daily amount and character of expectoration, and, once a week, the weight of the patient. If temperature keeps up, if the amount of pus continues the same or increases, or if the patient continues to lose weight, an attempt should be made at all risks to reach and drain the abscess from the outside. If temperature remains normal, if pus gradually or intermittently decreases, and if the body-weight is maintained or increases, operation is unnecessary, or, at all events, should be deferred.

Medicinal treatment with full doses of ipecacuanha and emetine,

maintained over a long period, generally exerts an instantaneous and almost miraculous effect upon these cases, and renders operative interference inadvisable.

In exploring the liver in such cases, it must be borne in mind that most likely the abscess cavity is collapsed, and that the sides of the abscess may be in contact. Such an abscess is not likely to be discovered unless the needle be thrust in to its full extent and, whilst a good vacuum is being maintained in the aspirator, slowly withdrawn. If by good fortune the abscess has been traversed, then, when the end of the needle is crossing the cavity, a small amount of pus will be seen to flow.

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened at once and treated on general surgical principles; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

Prognosis.—The prognosis in early operations on single abscess of the liver, provided there is no dysentery or other complication, is good. In multiple abscess, or in single abscess if there is active dysentery or other serious complication, the prognosis is bad; if there are more than two or three abscesses, it is usually hopeless.

The *question of return to the tropics* after recovery from liver abscess frequently crops up. If feasible, and if the patient has not to make too great a sacrifice, he ought to remain in a temperate and healthy climate. There are many instances, however, of individuals who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before giving permission to return it should be ascertained whether the bowel is thoroughly cleansed of amœbic infection. Neglect of this precaution may lead to reinfection from the bowel and recurrence of liver abscess after a period of as long as seven years from the formation of the first abscess.

2. AMŒBIC ABSCESS OF THE BRAIN

According to Armitage, 88 cases of amœbic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess. During life it gives rise to various cerebral pressure symptoms; and it is invariably fatal.

3, 4. AMŒBIC ABSCESS OF THE SPLEEN AND OF THE EPIDIDYMIS

Of these complications, the former is usually associated with hepatic abscess, but is rare. The latter has once been reported in a case from China by Warthin.

5. PULMONARY AMŒBIASIS

The type of case designated under this heading is quite distinct from those of pulmonary abscess secondary to the liver, in which infection of the lung tissue results as direct extension from the hepatic abscess or by actual rupture into the bronchus.

In primary pulmonary amœbiasis it is assumed that the entamœbæ reach the lung by direct embolism from the gut-wall. Having gained the pulmonary circulation, they form firm consolidated nodules, which later break down into small abscesses. The symptoms produced in these cases, of which the Editor has reported three, resemble closely those of a fugitive broncho-pneumonia or some form of tuberculous infiltration.

The patients who have been at some time the subjects of amœbic infection commence to suffer from pulmonary symptoms, with profuse purulent expectoration sometimes tinged with blood, and, it may be, respiratory distress and intermittent pyrexia. They are, however, subject from time to time to violent rigors, a feature

which serves to differentiate these cases on clinical grounds from other respiratory diseases which they may closely simulate.

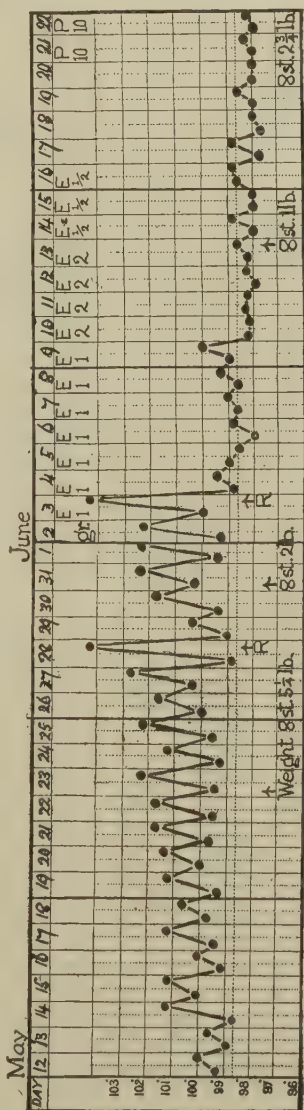


Chart 32.—Pulmonary amœbiasis with broncho-pneumonic symptoms and signs. Immediate improvement after institution of emetine treatment. (*Orig. case, from "The Lancet."*)

R = Rigor.

The physical signs produced in the lungs vary very much, but are usually those of broncho-pneumonic consolidation, patches of which are usually detectable at the border of the scapula, especially on the right side. Skiagraphy is of little avail in diagnosis. The entamœbæ have, so far, not been found in the sputum, though there is, as a rule, a distinct leucocytosis. The response to emetine or ipecacuanha treatment is as rapid as it is remarkable. (Chart 32.) A full course of emetine injections should be given.

BALANTIDIAL DYSENTERY

The occasional occurrence of *Balantidium coli* in the fæces, particularly in association with dysentritic diarrhœa, has been recognized for the last fifty years. It is only since Strong and Musgrave called attention to the subject that *Balantidium coli* has come to be regarded as the germ cause of a particular type of colitis resembling in many respects amœbic dysentery. The parasite has been studied zoologically, more especially in temperate climates, but it seems probable that extended observation will show that the balantidium is equally if not more prevalent in warm climates. Cases have been reported all over the world, but especially from Germany and France; those who tend domestic pigs are exceptionally liable.

How it attains the human intestine is not known, but as it is a common parasite of the pig and apes, in which it occasions a fatal form of dysentery, it is likely that one or other of these animals is the usual source of infection. Although the balantidium may live for a considerable time in water or fæces (one hour to three days), it has not been grown on culture media. In liquid stools it exhibits great activity, indulging in locomotive as well as in rotary movements.

For a description of the parasite, see p. 706.

Symptoms produced by balantidial dysentery are, in the present state of knowledge, indistinguishable from those of amœbic dysentery. The disease is chronic in type, its special nature being discoverable only on microscopic examination of the stools. Generally only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope.

In thirty cases in which autopsies have been made, a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, were found. On section, Strong demonstrated the balantidium, not only in exudate on the surface of the bowel, but congregated in large numbers in the follicles, and embedded in the tissues forming the base of the ulcerations, including the submucosa and muscular coat, and even in the lumen of blood-vessels and lymphatics. Bowman stated that the colon may be affected throughout its whole extent with a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amœbic dysentery.

Treatment.—Walker finds from his experimental work that organic compounds of silver are the most effective in eradicating the infection. Thymol, as in ancylostomiasis, has been recommended.

III. HELMINTHIC DYSENTERY

Bilharzial dysentery.—Adeno-papillomata or ulcerations of the large intestine caused by the passage of eggs through the

coats of the intestinal wall, occur in infections with *Schistosoma mansoni*, *S. japonicum*, and exceptionally with *S. hæmatobium*. The form of dysentery produced by these lesions is met with in those countries in which these parasites occur.

The stools typically contain yellow or bile-stained mucus with clots or streaks of blood, in which the eggs can be found under a low power of the microscope. Eosinophilia in the blood, together with symptoms of dysentery, is highly suggestive and the diagnosis should, if possible, be confirmed by the discovery of the characteristic eggs in the fæces. A sigmoidoscopic examination will help in doubtful cases. In making a microscopic examination of the fæces, the pathologist should remember that the eggs are more easily found in the outer zone of solid fæces than in more fluid portions (see p. 877).

Infection with *Cæphalogostomum apiostomum* (p. 762).—This is an intestinal parasite of man in northern Nigeria and Central Africa. but when present in large numbers it gives rise to dysenteric symptoms. The adult worm encysts under the submucosa, and may, together with its eggs, be recognized in the dysenteric discharges.

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of all the different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Double infections of amœbic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries, nor during the course of severe epidemics of bacillary dysentery. Usually, bacillary infection supervenes upon a long-standing amœbic ulceration of the bowel. It is a rare event to recognize pathogenic entamœbæ in a dysenteric stool and to isolate dysentery bacilli from the same specimen.

Bacillary dysentery occurs commonly as a terminal event in intestinal schistosomiasis, and amœbic ulcers are sometimes recognized as a concurrent infection in the same condition.

“*Giardia enteritis*.”¹—In addition to *E. histolytica*, *E. coli*, and *Balan- tidium coli*, certain other protozoa occur from time to time in the intestinal canal and appear in the fæces. Of these, perhaps *Giardia* (*Lamblia*) *intestinalis* has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine. When newly passed in the fæces it is very active, presenting a characteristic appearance. During

¹ *Giardia enteritis* is mentioned in this section for the sake of completeness, although the diarrhoea associated with the parasite cannot strictly be classified as a dysentery.

the passive stages the cysts appear in the fæces in enormous numbers. They are generally found in the fæces of about 7 per cent. of normal natives of the tropics. For a description of the parasite, see p. 695.

Giardia infection is associated at times with a type of recurring diarrhœa accompanied with abdominal discomfort. The stools may be of a peculiar clay colour and of a pultaceous consistence. On recovery from one of these attacks only the encysted form of the giardia can be found. Relapses of a periodic type tend to occur, but eventually tolerance of the parasite appears to be acquired. The attack is not accompanied by emaciation, and symptoms are thought to be due to the mechanical action of the parasite, and not to an actual lesion of the mucosa; though in mice, in which these parasites cause diarrhœa, they may be found in the submucosa in sections of the gut. Giardia infections are especially intractable and may persist for years; no drug has, so far, been found effective in ridding the intestine of these parasites.

In this country and in Canada the parasite has been found in the intestine of a large percentage of normal children, while Boyd, Silverman, and others have shown that it can be found quite commonly in the duodenal juice removed by Einhorn's tube, as well as in the bile; it has also been recorded in the gastric contents.

In the treatment of this condition emetine, E.B.I., and stovarsol have all been tried without effect. In the Editor's experience the only drug which has been a temporary effect of banishing the parasites from the fæces is yatren, given by the mouth as well as injected into the rectum. It is, however, extremely difficult to be certain that complete extirpation has been procured, for Giardia frequently reappear in numbers in the fæces after an absence of several months.

OTHER FORMS OF DIARRHŒA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, *Trichomonas intestinalis* and *Chilomastix mesnili* (see pp. 694, 693), though occurring commonly in diarrhœic and dysenteric stools, have little claim to pathogenicity; they are frequently present in large numbers in the fluid fæces of patients convalescing from bacillary or amœbic dysentery. No drugs have, so far, been found to have any lasting effect upon these protozoal infections.

Spirochætal dysentery is said to be due to the presence of numbers of spirochaetes in the intestinal canal. These organisms are composed of three or more simple spirals, and are known as *Spirochaeta eurygyrata*. They are frequently met with in dysenteric fæces, but there appears to be no valid reason for regarding them otherwise than as a concomitant infection superimposed upon amœbic ulceration of the intestinal canal.

"Malarial dysentery."—A blood-stained discharge, or more frequently an intestinal hæmorrhage, may occur in the abdominal forms of subtertian malaria; the blood passed is very dark, due to petechial hæmorrhages into the intestinal mucosa. These are very serious cases. Instances have been recorded in which malaria was first suspected from the discovery of the parasite within the red blood-corpuscles passed per rectum. Besides the hæmorrhagic appearance of the fæces, the clinical aspect of the patient, the

sweating, the icteric tint of the sclerotics and skin, and the enlarged spleen should suggest malaria.

"Kala-azar dysentery."—Blood and mucus may be passed in the fæces in advanced cases of this disease; this is said to be due to an actual ulceration of the bowel by the Leishman-Donovan body. The parasites are present in large numbers in the villi of the small intestines, and may even form polypoid masses in the mucus membrane of the large intestine.

Other conditions which may resemble dysentery.—There are other, perhaps more familiar conditions, not necessarily of tropical origin, in which dysentric symptoms may occur. They must be briefly mentioned.

Of all familiar diseases with which dysentery of a mild form is confused, the first place must be given to *internal piles*. Of course, in this instance a correct diagnosis is readily made. Again, profuse offensive diarrhœic motions with blood and mucus may be passed in *tuberculous ulceration* of the large bowel. *Colitis*, of both the ulcerative and *hæmorrhagic* varieties, resembles amœbic dysentery in clinical features and in the character of the stools, but can easily be differentiated by the microscopic examination of the fæces, as well as by means of the sigmoidoscope. Stercoral ulceration produced by chronic constipation, and often associated with myxœdema, may give rise to a blood-and-mucus discharge. Certain surgical conditions—*simple polypus*, malignant stricture, intussusception or even syphilitic disease of the rectum, the diagnosis of which is easily determined by a digital examination—should be kept in mind.

CHAPTER XXV

SPRUE

Synonyms.—Tropical Diarrhœa; Aphthæ Tropicæ; Psilosis; Ceylon Sore Mouth.

Definition.—A peculiar and very dangerous form of chronic catarrhal inflammation of the whole or part of the mucous membrane of the alimentary canal. Although a disease of warm climates, it may develop for the first time in temperate countries; only, however, in individuals who have previously resided in the tropics or subtropics.

Geographical distribution.—South China, Manila, Cochin China, Java, the Straits Settlements Ceylon, India, the West Indies, the southern United States, Porto Rico, and Queensland. Authentic records of sprue in North and Central Africa, Palestine, and Arabia are rare.

Epidemiology and endemiology.—Information so far amassed on this subject points to sprue being a regional, as opposed to a climatic disease, and it is one which pre-eminently affects Europeans. Doubt was formerly expressed as to the existence of sprue in native races, but this doubt is no longer held to be valid. The fact is that dark-skinned people, usually the indigenous inhabitants of the endemic country, are less liable to be attacked than are immigrant races.

The disease is often apt to occur in one or more members of the same family. Many instances of sprue developing in husband and wife have been recorded; it is probable that both have been exposed to the same influences. Atmospheric temperature does not influence the incidence of the disease, for sprue originates at high altitudes in Ceylon and in the Himalayas where the climate resembles that of Europe. There are residences in Bombay and bungalows in Ceylon which are notorious for the incidence of sprue in successive tenants, and the term "sprue houses" has been applied to them.

As a rule, sprue attacks those of middle age, but it has been recorded in children of 13. Amongst Europeans, at any rate, the female sex is more prone to the development of the disease.

Etiology.—A yeast fungus was described by Kohlbrügge in 1901 as the cause of the disease. It is probable that this represents merely a secondary or terminal infection, for in two acute cases ending fatally the Editor was unable to find it at all. Ashford, in Porto Rico, believes it to be a particular form of yeast fungus which has certain distinct morphological and cultural characteristics; on these grounds it has been named *Parasaccharomyces ashfordi*, or *Monilia psilosis*.

Some believe sprue to be a food-deficiency disease, due to absence of certain vitamins in the dietary. A condition resembling sprue has been produced by MacCarrison in monkeys fed upon a vitamin-free diet.

Scott's hypothesis.—H. H. Scott, impressed by the similarity between many of the symptoms of sprue and those occurring in other diseases in which calcium deficiency and a disordered calcium regulation play a part, suggested that the essential factor was a calcium deficiency. Such symptoms as tetany, cramps, loss of weight, and cedema, which may be present in sprue, lend a certain amount of support to his fundamental idea.

According to Vines, calcium occurs in the blood in two forms—the “combined” (or “coagulative”) and the “ionic”—and it is the latter that is deficient in gastric, duodenal, and varicose ulceration, while the regulation of ionic calcium is controlled by the parathyroid glands. As to the factors which bring about this calcium deficiency in the first instance, no satisfactory explanation has been forthcoming, though it is suggested that hyperacidity of the gastric juices, due to a highly nitrogenous diet leads to habitual hyperacidity, and with it over-production of *secretin* in the duodenum, leading to over-stimulation of the pancreas, and therewith to an over-balance of other endocrine glands, as the salivary and parathyroids. The ultimate result is an intestinal toxæmia and the familiar symptoms of sprue. This hypothesis has already received some support from the published analyses of the blood-serum in cases of sprue, in which the amount of free calcium has been found to rise from 6 to 10 mg. per 100 c.c. of serum after the administration of calcium lactate over a considerable period (the normal being 10·5–11·5).

Fairley and Mackie, as a result of combined clinical and pathological observations, regard sprue as definitely due to some infective agency which especially involves the mucosa of the alimentary canal. Instances of multiple infection in the same family have been noted in certain bungalows and localities.

In the Editor's experience there is a considerable amount of evidence of the close association between sprue and amœbic dysentery. The two diseases often co-exist, while on occasions sprue appears to be grafted on intestinal amœbiasis. Possibly sprue is a syndrome primarily caused by amœbic ulceration of the small intestine. Possibly, too, in the apparent absence of this disease from Central Africa may lie the clue to its true etiology.

Pathology.—Post mortem, the tissues in sprue are abnormally dry; fat is almost completely absent; the muscles and the thoracic and abdominal viscera are anæmic and wasted. The liver is atrophied to half its normal weight, or even less; the spleen, adrenals, heart, and in fact all the viscera, are wasted approximately to the same degree. With these exceptions and

certain important changes in the alimentary tract, so far as known there are no special lesions which are invariably associated with this disease. Occasionally certain changes are present in the pancreas—namely, fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of the tongue show desquamation of the epithelium, especially from the surface of the fungiform papillæ, which may be infiltrated with yeast fungi.

Lesions of the alimentary tract.—The principal and characteristic lesions are found in the alimentary tract. The bowel is thinned to such an extent as to be almost diaphanous. The serous coat is generally healthy, the muscular coat atrophied. The internal surface of the bowel is coated with a thick layer of grey, tenacious mucus which conceals patches of congestion, of erosion, or even of ulceration, besides such evidences of similar antecedent disease as pigmented areas and thin-scarred, cicatricial patches. In two cases under the Editor's care, death resulted from perforation of an ulcer or ulcers in the ileum and purulent peritonitis. The ulcers in these cases extended throughout the jejunum and ileum, and were in some cases superficial, in others deep, but surrounded by a zone of atrophied and diaphanous mucous membrane. The villi and glands are eroded, and in many places completely destroyed. Here and there minute spherical indurations, about the size of a pin's head and surrounded by a dark pigmented or congested areola, can be felt in the mucous membrane. On cutting into these, one finds them to be minute cyst-like dilatations of the follicles filled with a gummy, muco-purulent material. Sections of the diseased bowel show under the microscope corresponding changes, such as varying degrees of erosion or ulceration of the surface of the mucous membrane; degeneration of villi, glands, and follicles; the small mucous cysts referred to; sometimes small abscesses; also, infiltration by leucocytes of the basement membrane and submucous layer; and, in the latter, fibro-cirrhotic changes (Fig. 81). The mesenteric glands are generally large and pigmented, perhaps fibrotic. The erosive lesions are usually most marked towards the end of the ileum and in the colon; but they may be present in greater or less degree universally, or in patches throughout the entire alimentary tract from mouth to anus.

In the Editor's opinion the essential pathological lesion lies in the destruction, total or partial, of the intestinal villi of the ileum by a process of superficial ulceration, leading to inability to absorb the predigested fats, and thus giving rise to the characteristic stools and other phenomena.

Analysis of the stools in sprue reveals the presence of the ordinary elements of bile, notwithstanding their apparent absence as indicated by lack of colour. Bile is secreted, but the colouring matter, bilirubin, is not formed, as is normally the case, by bacterial action, but is reduced in the intestine to a colourless substance, urobilinogen. The excess of fat in the stools and low fat content of the blood (412.8 mg. per cent.) would indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mg. per cent.)

Normally, neutral fats are to fatty acids in the proportion of 1 : 2; in pancreatic disease this ratio is reversed, and may be as high as 15 : 1; while in sprue stools more splitting-up of fats takes place, the proportion of neutral fats to fatty acids being as 1 : 3 or even 1 : 5 (J. D. Thomson). These figures indicate



Fig. 81.—Transverse section of ileum in case of sprue, showing partial loss of columnar epithelium (probably a post-mortem change), shrinkage of villi, round-cell infiltration, fibrosis of submucosa, and dilatation of nutrient vessels of submucosa. (*Orig.*)

that in sprue the pancreatic digestion proceeds quite normally but that the products of this digestion are not absorbed.

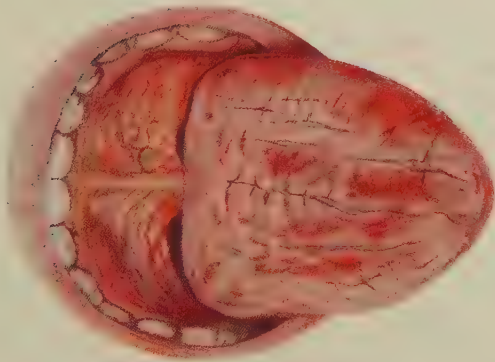
Symptoms. Variability.—There is infinite variety in the combination and in the severity of the various symptoms of sprue, as well as in the rate of progress of the disease. In some instances it may be almost a subacute process running its course in a year or two; in others, again, it may drag on intermittently for ten or fifteen years. Much depends in this respect on the circum-

stances, the character, the care, the treatment, the age and the intelligence of the patient.

General symptoms in a typical case.—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms: soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels; the last being particularly urgent during the early morning and part of the forenoon. The patient may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable.

Mouth lesions.—If the mouth is examined, the soreness will be found to depend on a variety of lesions of the mucous membrane, which, though painful, seem to be of a very superficial character. These lesions vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry; superficial erosions, patches of congestion, and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, the sides of the organ have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform papillæ may stand up, pink and swollen. (Plate XXV.) If the patient be made to turn up the tip of the tongue, very likely red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may be seen on either side of the frænum. On eversion of the lips, similar patches and erosions are visible; and if the cheek be separated from the teeth, the same may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected; very often in this situation the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore.

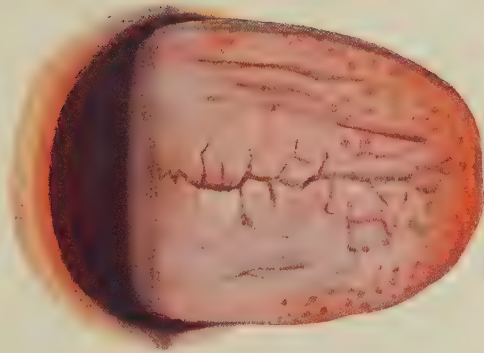
In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the sternum, suggesting that the gullet, like the tongue, is also in an irritated, raw, and tender condition. During exacerbations of the disease



Acute stage. (*After Thin.*)



Acute stage with typical aphthae.
(*P. H. Manson-Bahr, del.*)



Chronic stage.
(*P. H. Manson-Bahr, del.*)

SPRUE TONGUES.

PLATE XXV

the condition of the mouth becomes greatly aggravated. Although during the temporary and occasional improvements it is much less painful, even then salt, spices, strong wines, and all kinds of sapid foods sting unpleasantly; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur; during the exacerbations it is red and swollen; but during the remissions, and when not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish like a piece of cartilage. Apparently the tongue condition may be the sole symptom, and may persist for years before the characteristic diarrhœa supervenes.

Dyspepsia.—Dyspepsia is usually much complained of, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel. Occasionally, though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by feelings of nausea. (Fig. 82.)

Anæmia may be pronounced, sometimes even in the early stages of the disease, but more generally it develops when the diarrhœa has persisted for some time. It may be very profound and may approach the pernicious type, with alteration in the size and shape of the erythrocytes and the appearance of normoblasts. It is apparently secondary to an intestinal toxæmia, but sometimes a true Addisonian anæmia supervenes after all active symptoms of sprue have disappeared; such cases are invariably fatal.

The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilin and urobilinogen in pathological amounts, derived from the products of blood destruction. It is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times as rapidly as in a normal man.

Tetany associated with dilatation of the stomach has been recorded in the terminal stages of chronic sprue.

Cramps in hands and legs may be a particularly distressing feature in an advanced case of the disease.

Diarrhœa.—The diarrhœa associated with sprue is of two kinds—one chronic and habitual; the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material; the latter is of a watery character, also pale and fermenting, the dejecta containing un-

digested food and, as a rule, an abnormally large amount of oil and fatty acids. In these latter circumstances the diarrhoea usually brings with it considerable relief to the dyspeptic distension, at all events for a time. When the mouth is inflamed the diarrhoea is usually more active, but this is by no means invariably the case. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent phase,

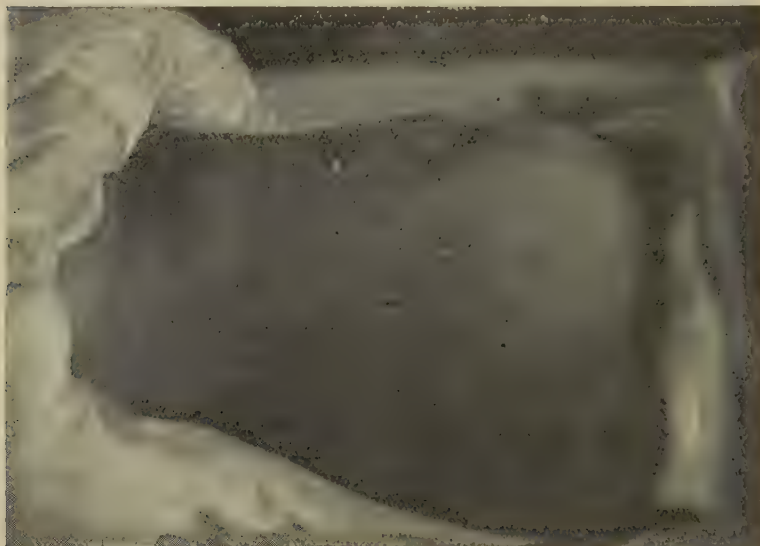


Fig. 82.—Sprue abdomen, showing intense meteorism, especially of lower quadrant. (*Orig.*)

however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to the aforementioned excess of fat and to the innumerable microscopic gas-bubbles; patients remark their phenomenal abundance. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, excoriated condition of the anus, and sometimes, in women, a similar condition of the vagina.

Types, history, course, and termination. *Protopathic sprue.*—There is a striking uniformity in the history of most cases of sprue. On inquiry, we shall probably learn that the patient has been suffering for months, or perhaps years, from irregularity of the bowels. This, we may be told, began soon after arrival in the

tropics as a bilious morning diarrhœa. For a long time this morning diarrhœa went on, without interfering in any way with the general health. Later, the mouth, now and again, became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhœa. Gradually the stools lost their bilious character and became pale and frothy; dyspeptic symptoms, particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently and in a more pronounced form, following, almost inevitably, any little imprudence as regards food or exposure. The general condition now began to deteriorate; emaciation, languor, lassitude, and inability to get through the day's work satisfactorily becoming more pronounced each summer until, finally, a condition of permanent invalidism was established. Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhœa may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very dark; the appetite, sometimes in abeyance, is more frequently ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhœa. At length the patient is confined to the house, perhaps to bed. The feet become œdematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally, the patient dies in a semi-choleraic attack; or from inanition; or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Sprue secondary to dysentery.—When the disease has supervened on dysentery, usually amœbic, we learn that the motions characteristic of the original dysenteric attack had gradually changed in character; from being scanty, mucoid, bloody, and accompanied with pain and tenesmus, they became diarrhœic, pale, frothy, their discharge being followed by a feeling of relief rather than of pain. The mouth at the same time became sore, exhibiting the characters already described. Gradually a condition of confirmed sprue is established, which ultimately, unless properly treated, will almost certainly prove fatal.

Sprue secondary to acute entero-colitis.—Another type of case commences as an acute entero-colitis or hill diarrhœa, with sudden and profuse colicky diarrhœa, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely,

but gradually have the typical symptoms of sprue grafted on to those of an acute intestinal catarrh.

Incomplete sprue. (a) *Gastric cases.*—Occasionally we meet with cases of confirmed sprue in which, at first, the morbid process, judging from the existing clinical symptoms and subsequent history, is confined to a limited part of the alimentary canal. Thus we sometimes get sprue without diarrhœa, the principal symptoms being sore mouth, dyspeptic distension, pale, copious, but solid stools, and wasting.

(b) *Intestinal cases.*—On the other hand, we may get cases in which the mouth is not eroded and there is little or no distension or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient, who may have suffered at an earlier period or on a former occasion from the first type of the disease, later acquires the diarrhœic form; and vice versa.

(c) *Sprue without diarrhœa.*—It sometimes happens that under treatment the sore mouth, the dyspepsia, and the diarrhœa completely subside; nevertheless, the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition.

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside; but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Latency.—One of the most remarkable things about sprue is the latency of the process. The disease may arise in England in persons who have at some time resided in an endemic area of the disease: usually this period is one or two years; sometimes it is longer—seven or eight years; exceptionally the latent period may be as long as twenty-five years; and rarely, as in one instance on record, forty-six years.

Diagnosis.—The condition of the tongue, the character of the stools, and the history are sufficiently distinctive, one would suppose, to render diagnosis an easy matter. Nevertheless, we have known of cases in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed

to this disease, and the character of the stools and other symptoms being ignored. Care must be exercised in interpreting the significance of the small area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to the wasting the liver undergoes in common with the rest of the soft tissues of the entire body. The absence of skin lesions and mental symptoms differentiates sprue from pellagra. No difficulty should be experienced in differentiating the sprue tongue from that of pellagra; in the latter disease it is pointed, and when it is inflamed and painful the process is found to be generalized over the whole organ, and not confined to certain definite and circumscribed areas as in sprue. It is necessary to remember that atrophy of the lingual papillæ occurs in pernicious anæmia and even in malarial anæmia and ancylostomiasis, diseases which may be confused with sprue.

According to Thaysen the low blood-sugar curve after the intake of 1 grm. of glucose per kilo body-weight serves to differentiate sprue from pernicious anæmia and allied conditions.

The differentiation of sprue from chronic pancreatitis may present difficulties. In the latter condition the neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high. The anæmia greatly resembles that of true Addisonian anæmia, though normoblasts are rare in the blood of sprue and megaloblasts do not occur. High Van den Bergh readings are the rule in true pernicious anæmia, exceptional in sprue. Certain cases of *tabes mesenterica* may, on clinical grounds, resemble sprue.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for long-standing cases, for careless and injudicious patients, and for those who cannot or will not take a diet composed mainly of milk.

Treatment.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally marvellously successful. Should, however, it be undertaken at too late a period, when the glands and the absorbing surface of the alimentary canal have been hopelessly destroyed, do what we will the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing for the physician to do is to get his patient thoroughly convinced of the deadly nature of his complaint; for, unless he receives the patient's hearty and complete co-operation, he must not expect to cure a well-established case. To be successful, treatment must be

thorough, sustained, and prolonged. All predisposing causes, as uterine or other discharges, syphilis, scurvy, and the like, must, of course, be dealt with and, so far as possible, removed. The size and weight of the fæces should be estimated daily by weighing the pan and subtracting from the total the known weight of the receptacle. The average daily weight of normal fæces is from six to eight ounces; in sprue it is commonly double or treble this. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

The nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so that the nurse will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be adopted and strictly adhered to both in quantity and ingredients.

The milk cure.—By far the most successful treatment is what is known as the milk cure. In carrying this out it is well to commence with a dose of some aperient—castor oil or pulvis rhei compositus. Pending the action of the drug, all food, including milk, should be withheld. The patient should be sent to bed in order to economize strength and maintain equable warm temperature of the skin. He should also be directed to clothe warmly, to encircle the abdomen with a broad flannel binder, to cover his arms and shoulders with a warm jacket, and to live in a large, sunny, warm room. When the purgative has acted the milk is begun. At first 70 oz. at most are allowed in the twenty-four hours, eight-ounce feeds being given every hour or every two hours. When the patient is very weak the feeding must be continued during the night. *The milk should not be drunk, but sipped with a teaspoon, or taken through a straw or a fine glass tube, or from a child's feeding-bottle.* As a rule, on this regimen, in the course of two or three days, the patient's condition is very much improved. The stools have increased in consistence—are solid, perhaps—the distension of the abdomen has subsided, dyspeptic symptoms have vanished, and the mouth is much less tender and less inflamed. The quantity of milk should now be increased at the rate of half-a-pint a day or every second day, until 100 oz., or thereabouts, are taken in the twenty-four hours. It is well to keep at this quantity for ten days at least, when, everything going well, a gradual increase to 6 or 7 pints may be sanctioned. If the patient gets weary of milk, Benger's food forms an efficient substitute. Very often patients prefer this to milk, and, in order to vary the monotony, it is often wise to give it in alternate feeds with pure milk. Being predigested,

Benger's food is particularly well borne by sprue patients; moreover, the preparation is palatable. Some patients, unable to tolerate milk, thrive on "Benger's" or "Horlick's." Up to this point the patient should keep in bed; but when he is able to take 6 or 7 pints of milk he may get up and, if he feels strong enough and the weather is mild, go out of doors. *For six weeks, dating from the time the stools become solid and the mouth free from irritation, no other food or drink whatever should be permitted.* A raw egg, if it is found to agree, may now be added to the milk; later, some artificial malted food; next, small quantities of well-boiled arrowroot, rusks, pulled bread, thin bread (stale) with a little butter, or some digestible form of biscuit; later still, chicken broth, and a little fruit; and, by and by, fish and chicken may be gradually introduced. To some patients the milk is made more palatable by the addition of a pinch of salt to each glass.

Importance of prompt treatment of threatened relapses.—Should, however, the slightest sign of dyspepsia or flatulence, especially of diarrhœa or of sore mouth, show itself, then the extra food must be discontinued immediately, a dose of compound rhubarb powder or castor oil administered, and the patient be sent back to bed and placed once more at absolute rest and on a strict milk diet. In convalescents, no matter how long the acute symptoms have been in abeyance, this prompt recognition and treatment of threatened relapse should be rigorously observed. This is a rule of the utmost value and importance. Procrastination in treatment, under these conditions, is exceedingly dangerous. Promptitude in recognizing and treating relapse not only saves time, but may avert hopeless intestinal atrophy.

Symptoms persisting.—In commencing this treatment, if the patient, after two or three days, be found unable to digest and assimilate so much as 3 pints of milk in the twenty-four hours, the daily allowance must be reduced by half-a-pint a day until only 30 oz. or thereabouts are taken. If now the motions become solid, the quantity of milk may be gradually increased by 5 or 10 oz. a day, so that in the course of a few weeks the full allowance—6 or 7 pints—is consumed. In cases with persistent dyspepsia, pancreatic preparations, such as Savory & Moore's pancreatic emulsion, or taka-diastase may be of benefit. Milk may occasionally be made more digestible and tolerable by the addition of bovril in the proportion of one teaspoonful to every 8 oz., or by being beaten up with the yolk of an egg. The preparation known as marmite, given in teaspoonful-doses dissolved in water or milk, is occasionally of benefit.

How to meet inadequate assimilation.—It sometimes happens that the quantity of milk can be raised to 70 or 80 oz. per diem, but no higher, further increase bringing on sore mouth, distension, and diarrhoea. In some of these cases the difficulty appears to depend not so much on digestion as on inability to absorb a large quantity of fluid. Occasionally, in such cases, one may succeed in getting the necessary amount of nutriment introduced by thickening the milk with condensed milk, or by slowly evaporating fresh cow's milk so as to reduce its bulk without diminishing the solids (Thin). The evaporation is best done in a vessel like a glue-pot, in which the milk is not boiled but is surrounded by a jacket of boiling water; the milk during the process must be constantly stirred to prevent the formation of a scum. Or the milk diet may be supplemented by an adequate allowance of raw or underdone meat, by Valentine's meat-juice (1 dr. in 3 oz. of water), or Brand's essence in teaspoonfuls, given two or three times a day. Rice-water, boiled for two hours and strained, 8 oz. per day, is agreeable to many patients, and easily tolerated.

Other forms of giving milk.—Digestion is sometimes aided by peptonizing the milk; or by mixing it with lime-water or a little salt; or by aerating it in a soda-water siphon. Koumiss or *yag-hourt* (sour milk), sometimes agree for a time when ordinary milk fails, and, if necessary, should be tried. Similarly, white wine whey is occasionally digested when milk is not; it is often of great service, especially when an alcoholic stimulant is indicated.

Constipation.—Usually in milk treatment the fæces become hard and scybalous, and the patient suffers much from distension. In these circumstances castor oil, in drachm-doses, should be given in liquid form or in cachets. As a general rule, this immediately relieves the condition. The routine administration of medicinal paraffin in teaspoonful doses is sufficient to keep the motions from balling. *Petrolagar*, or *agarol* (preparations of liquid paraffin and agar), given in teaspoonful to tablespoonful doses, are particularly suitable for sprue patients. Flatulency is best counteracted by small doses of castor oil, by hot baths and by restricting the amount of food. Pituitary extract preparations, such as kinazyme tablets, are useful in expelling the flatus.

Fruit treatment.—The value of fruit in the treatment of sprue and other forms of intestinal disease has long been recognized by practitioners. Manson had long been in the habit of prescribing bananas and apples, tentatively, of course, in sprue, and often with marked success. Of late, repeated trials of the strawberry in sprue have confirmed one's personal belief in the value of this

fruit treatment, and in the strawberry treatment in particular. The plan Manson followed was to give one or two strawberries with each feed of milk, and, if found to agree, to increase the number gradually until 2 to 3 lb. were taken daily. Preserved bottled fruits, particularly peaches and pears, make suitable substitutes if strawberries or bananas are not obtainable. Fresh raspberries and blackberries, when eaten in the same way, are almost as well tolerated as are strawberries. A dietary of fresh tomatoes is often beneficial. The bael fruit or Bengal quince (*Ægle marmelos*), introduced by Fayrer in the treatment of this disease, seems to exert a very beneficial effect in the countries (Ceylon and India) where it can be procured in a fresh state. Of recent years it has been imported from the East on ice, and offered for sale in London. Extracts of bael, such as those sold in this country, appear to be inert. The ripe pulp should be scraped out of the hard exterior shell and eaten raw with sugar and cream, or made up with gelatin in the form of a jelly. Two or three of these fruits, depending on their size, may be given every day.

Treatment with meat juice and underdone meat.—Occasionally, especially in elderly patients, symptoms persist or become aggravated under the system of treatment described, and one is forced to conclude that milk does not suit the patient. Some patients cannot tolerate milk; it may cause nausea or even acute intestinal discomfort. In such cases raw-meat juice will often prove an efficient substitute. The juice of 4 or 5 lb. of fresh lean meat, with a little water to allay thirst, may be taken in small quantities at short intervals daily. After a time, when the stools are reduced in number and amount, although perhaps not quite solid, scraped meat, or very much underdone meat, and by and by a little charred toast, a plain rusk or biscuit, and so forth, may be gradually added to the diet.

Raw meat sandwich.—Quarter-of-a-pound of best beefsteak, free from fat, is cut into small pieces and passed through a fine mincer. Two thin slices of bread are toasted slowly so that they can dry right through. Pepper and salt are added to the minced meat, which is placed between the toast and eaten. For those who cannot tolerate it raw, the meat may be slightly done: 1 lb. of tender undercut or beefsteak should be shredded finely, and all fat and gristle removed with the end of a blunt knife; then a tablespoonful of water should be added for every 4 oz. of meat, with a little salt and pepper. This mixture should be placed in an iron pan and stirred over the fire till just brown in colour, for a period of seven to ten minutes; it should then be served with a piece of dry toast. A slice of steamed tomato adds to the palatability of the dish.

Liver soup, made from fresh calf's-liver, when procurable, or from ox-liver, has acquired a very considerable reputation in the

treatment of sprue. For this purpose it is necessary that the "soup" be specially prepared.

Three quarters of a pound of liver are taken, finely minced, and immersed in one quart of water, to which, when boiling, are added a teacupful of tapioca and the necessary amount of pepper and salt. After simmering for *three* hours, the resulting fluid is strained off and sipped slowly. Eight to sixteen ounces may be given daily. For those persons who cannot tolerate raw meat the appearance and taste of the meat pulp may be disguised by adding it to the soup. Marmite—one drachm—may be added to each cupful of soup.

In the Hospital for Tropical Diseases, in London, liver soup is regarded as almost a specific in sprue, and as being more easily tolerated than any other form of dietary. The soup will not keep, and must be prepared daily. This treatment has been recognized for over thirty years and is of special interest at present in view of the work of Minot and Murphy in America on the effects of a liver dietary in pernicious anæmia in which 3 to 8 oz. of lightly-cooked or raw liver are eaten daily.

Meat and warm water diet.—Not infrequently, after the stools have become solid under a carefully regulated strict milk diet, it is found that any attempt to return to ordinary food, or to take anything beyond the most simple farinaceous dishes, is quickly followed by a recurrence of diarrhoea and the familiar flatulent dyspepsia. Such cases are sometimes successfully treated by a complete abandonment of milk, fruit, and farinaceous stuffs for a time, and placing the patient on what is known as the "Salisbury cure," which consists of taking the meat, prepared as above, gradually increasing to 1 lb. daily, together with warm water amounting to 4 pints in the twenty-four hours, drunk before going to bed and on rising in the morning, and also about two hours before meals—never at meals. This course must be persisted in for six weeks, when ordinary food may be gradually attempted again.

The Editor has sometimes found it useful, in cases of relapsing sprue, to make the patient fast systematically one day a week, feeding him on that day with milk only. Sometimes, in cases of active sprue, he has found benefit from intermitting the strict milk diet for a day or two every week, and on these days feeding the patient on minced meat and hot water only.

Nutrient enemata or suppositories.—In all grave cases of sprue, nutrient enemata or suppositories should be steadily administered every four or six hours. If tolerated, they are most valuable aids to nutrition. It is well, when using them, to wash out the rectum once a day with cold water.

These methods of treatment—followed by a carefully selected and increasing mixed diet, combined with warmth and rest—are the most successful ways of dealing with sprue; should they fail, the chances of recovery are poor indeed. Nevertheless, we have seen cases in which, after failure of the most carefully carried out milk or meat diets, a mixed diet proved successful for a time. In such mixed diets, in fact in all diets in sprue, *restriction in the amount* is as important, perhaps, as the nature of the food consumed. Food should never be given unless the patient is hungry. It is a great mistake to try to make these patients fat rapidly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

Each case must be treated on its merits, for no absolutely infallible rules can be laid down. Some patients, owing to an inherent dislike of milk, do badly on that diet from the start. Attempts to force them merely result in the abolition of that co-operation between patient and doctor which is so essential to success. The Editor is in the habit of gradually adding toast, rusks, chocolate, an egg, and other more palatable items to the diet directly the *fæces* become reduced in amount and are of a moderate weight. All sources of *mental* worry should be eliminated if possible; the attention of over-anxious relatives is not to be encouraged; therefore, in practice, cases do best under the strict discipline of hospital life.

CALORIE VALUE OF THE DIETARY

The calorie value of a *commencing* sprue dietary should be about 1,800 made up as follows:

Milk (3 pints)	1,140 calories
Rusks (4oz.)	280 "
Sago (2 oz.)	204 "
Liver soup (16 oz.)	180 "

On discharge, about 4,000 calories:

Milk (5 pints)	1,900 calories
Rusks (8 oz.)	560 "
Sago (8 oz.)	816 "
Liver soup (16 oz.)	180 "
Chicken (5 oz.)	165 "
Fish (3 oz.)	60 "
Two eggs (4 oz.)	172 "
Banana (2 oz.)	50 "
Orange (4 oz.)	52 "
Extra: Raw meat (4 oz.)	188 "

4,143 calories

When to send the patient to Europe.—When sprue develops in the tropics, if feasible the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or if his end is manifestly not very far off. Diarrhœa should not be active when the patient is put on board ship. In every case, provision such as a cow or an abundant supply of sterilized milk should be made for carrying on treatment during the voyage.

The clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics. If their return is during the winter, they should arrange to remain in the south of Europe till at least late spring. Next to an unsuitable dietary, perhaps cold is the most prejudicial influence to which a sprue case can be exposed. A sprue patient ought never to feel cold; he ought always to wear thick flannels, thick stockings, and, when up and about, thick boots. In winter a chamois-leather waistcoat provided with sleeves is of great service. His rooms ought to be warm. He ought to eat very sparingly. He ought never to be fatigued; he ought to go to bed early and rise late; in fact, he ought to do everything in his power to avoid irritating the bowel, to guard against chill, physiological depression, and the necessity for copious eating.

During the summer England is suitable enough as a residence; but during the cold winter and spring months some milder, drier, and more sunny climate must be sought out.

Drugs.—Experience soon teaches one to distrust medicines in sprue. Occasionally a gentle aperient is of service, or, if diarrhœa is watery and excessive, a few drops of laudanum; but active drugging of all sorts is, as a rule, in the highest degree prejudicial. The mouth should be kept scrupulously clean, and should be washed out after each feed with a bland mouth-wash, such as potassium chlorate, 1 drachm to the pint of hot water (or rose-water). If the mouth is very painful, cocaine—2 gr. to the ounce in glycerine and borax—brushed on before eating will deaden sensibility and, for a time at all events, relieve suffering. Should the saliva be very acid, an alkaline mouth-wash should be used. The following has been found very beneficial:

Sodium bicarbonate	.	.	.	gr. x.
Sodium biborate	.	.	.	gr. x.
Eau de Cologne	.	.	.	$\frac{1}{2}$ i.
Aq. ad	$\frac{3}{4}$ iv.

Scott's treatment consists in the administration of powdered

calcium lactate in cachets,¹ in a dose of 10–15 gr. after food, three times a day; diet should be strictly adhered to as already outlined, but should be increased in variety and quantity as early as possible. Parathyroid extract $\frac{1}{10}$ gr. is administered twice daily with the idea of regulating the calcium absorption. The administration of calcium lactate appears to exert a distinct therapeutic effect in alleviating flatulence.

This treatment should be instituted in the acute stage of the disease, and persisted in for several months during convalescence. It was at first considered that this treatment has a distinct influence in abolishing the more active symptoms of sprue, but it is now doubtful whether it has any prolonged therapeutic effect.

Chromosantonin (5 gr. in olive oil twice daily), or santonin, which by prolonged exposure to bright sunlight has become yellow, has been advocated by Begg, but there is no evidence that it exerts any specific action on sprue.

Repeated administration of purgatives alternately with or before the administration of carbonate of lime (believed to be powdered cuttle-fish bone or crab's eyes), 2 dr. at a time, has gained a local reputation in Shanghai. This preparation is now sold in this country as Batavia powder, or pulv. Bataviæ co., and is given in teaspoonful doses in 4 oz. of milk.

The Editor is of the opinion that Batavia powder administered regularly is of the greatest value in these cases, especially in elderly people, in whom the diarrhoea recurs in spite of strict dieting. In these cases it can be given in 15-gr. doses in cachets, three times daily and continued for several months. Crookes' collosol kaolin (1-dr. doses) acts much in the same manner as does Batavia powder.

For the anæmia, one may give intramuscular injections of 10 min. of a soluble preparation of arsenate of iron (Squire's), or the sérum ferrugineux (*Frais*se), containing cacodylate of iron (1–2 c.c.), at weekly or bi-weekly intervals. In some instances the benefit from these injections has been prompt and marked, and their employment in every case of sprue in which anæmia is pronounced is indicated.

No advance in the treatment of sprue has been more remarkable than the effect of blood transfusion in those cases in which the anæmia has become so extreme as to resemble the most desperate forms of Addisonian anæmia. The Editor regards this measure, so striking have the results been, as a cure, not only for the anæmia, but for the underlying sprue. Cases, especially in elderly people, who were at death's door from very advanced hæmolysis with a red blood-count as low as 500,000 red cells to the c.mm., and with a hæmoglobin-index hardly computable, have entirely recovered

¹ Calcium lactate may be prescribed as follows: 15 gr. to 4 fl. oz. of aq. chloroformi. Dissolve 200 min. dil. ac. lactic. in the same quantity of aq. chloroformi and slowly add to the mixture. In this manner calcium lactate can be exhibited in solution.

their health and strength. All special precautions (*see* p. 668) must, of course, be taken and 300–400 c.c. of blood injected intravenously. Experience has shown that it is not the *quantity* of blood that is the important factor. Sometimes 2 or even 3 transfusions at weekly intervals are necessary in order to restore the hæmatopoietic functions of the bone-marrow, and this is probably the manner in which blood transfusion acts.

Blood transfusion should be reinforced by the exhibition of *liquor arsenicalis* by the mouth, commencing with 1 min. three times daily and gradually working up to a maximum of 15 min. This treatment was first carried out in a series of cases under the care of the Editor, and has since been confirmed by others.

Flatulence and diarrhœa are sometimes relieved by massive doses of sodium bicarbonate, and by hot baths and packs, by charcoal biscuits or granulated charcoal, or by kaolin.

The sprue patient, if possible, ought not to return to the tropics. If compelled by circumstances to do so, he must exercise the utmost care with regard to his health, and avoid exposure, cold baths, alcohol, and all excesses; take a minimum of, or avoid altogether, red meat; purge gently, and go on absolute milk diet on the slightest sign of relapse.

Appended is a diet table which should serve as a guide for convalescent cases of sprue which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.

Well-boiled porridge (Quaker oats) or gruel. Sour milk (yaghourt).
Lightly boiled or scrambled eggs.
Kedgeree.
Filleted or steamed fish: haddock, plaice, turbot, cod, sole, or whiting.
Toast, rusks or biscuits.
Cocoa, weak tea,¹ or chocolate made with milk.
Butter in small quantities with bread or toast.

11 a.m.

Half-pint of warm milk.

Lunch.

Clear or liver soup or chicken broth.
Steamed fish.
Chicken boiled in rice.

Spinach, vegetable marrow, young peas, cauliflower, or french beans. Boiled onions.
Well-cooked milk puddings: sago, ground rice, semolina.
Baked apple or baked banana.

Tea.

Weak tea.
Toast.
Wafers, water or Marie biscuits.
Madeira cake.
Sponge fingers.

Dinner (7 p.m.).

Brains.
Sweetbread.
Fruit or calves-foot jelly.
Cornflour shape or arrowroot.
(*Dinner should be the lightest meal of the day.*)

¹ Sprue tea is best made with boiling milk in place of water.

*Suggested Diet for Convalescent Cases of Sprue (continued).—**Fruits permitted.*

Bael fruit, bananas, oranges,
 papaya, tomatoes.
 Ripe pears.
 Table apples (one a day).
 Strawberries, commencing with
 $\frac{1}{2}$ lb.; maximum, 3 lb.
 Raspberries, blackberries, logan-
 berries (as above).
 Hot-house grapes.
 Fruit jellies.
 Bottled fruit (not tinned), especi-
 ally peaches and pears.

Articles of diet to be avoided.

Salmon, trout, mackerel, herrings.
 Cheese.
 Fresh bread.
 Jams, especially marmalade.
 Grease or fat.
 Suet puddings.
 Nuts.
 Cakes with raisins.
 Potatoes in jackets or fried.
 Pastry of all kinds.
 Alcoholic drinks.
 Mineral waters.

Treatment of complications.—Careful search should be made for any coexisting infection from which the patient may be suffering and which is grafted on to sprue. Malaria, especially the benign tertian, is a case in point, or more important still, it may be, syphilis. Experience shows that, not only do sprue patients who are the subject of an old syphilitic infection, tolerate antisymphilitic treatment very well, such as potassium iodide and salvarsan, but that the sprue condition does not tend to improve until this has been undertaken. Sprue may be complicated by active amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodide may be necessary before any improvement in the sprue condition is noted. Acute appendicitis quite commonly complicates sprue. Not only do the patients tolerate appendicectomy extremely well, but the removal of the acutely inflamed appendix sometimes appears to cure the sprue. The Editor has observed several instances where the patient survived acute pneumonia and, after recovery from the acute infection, subsequently remained free from sprue-like symptoms.

Oral sepsis.—Bad teeth and pyorrhœa must be attended to after the subsidence of acute symptoms of sprue. Great care should be exercised; it is a great mistake to advocate too rapid extraction of teeth, as it is liable to provoke a serious relapse.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on their visiting the hills after residing for some time in the hot lowlands of tropical countries.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease, pointed out that a similar affection may show itself in the highlands of Europe as well as in those of India. It is said

to occur also in corresponding circumstances in South Africa and South America. There is no reason, therefore, to suppose that hill diarrhœa is special to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases happening within a week of each other. In some years hill diarrhœa is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without examples.

Etiology and pathology.—It is difficult to say what may be the precise factors determining this disease. The low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share. Manifestly there is a suspension of the functions of the liver, and, considering the dyspepsia and looseness, most probably of those of the pancreas and of the other glandular structures subserving digestion. Hill diarrhœa is certainly something more than an intestinal catarrh. As Crombie pointed out, it is more in the nature of dyspepsia. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa.

Symptoms.—Without very obvious cause the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half-a-dozen, or more, such stools may be voided before 11 A.M. After that hour—at all events, in ordinary cases—the diarrhœa is in obedience for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon; the absence of colour in the stools; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if some boiling or chemical operation were proceeding in his inside. Occasionally cases are met with in which the stools are very pale although there is no diarrhœa. In a certain proportion of cases, symptoms persist and develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin or ingluvin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXVI

TROPICAL LIVER

THE subject of liver disease is everywhere a difficult and complicated one. It is especially difficult in tropical countries; for not only is the resident there liable to all the forms found in temperate climates, but he is exposed, in addition, to various potent predisposing and exciting causes of liver disease not present, or only present in a very mild degree, in more temperate latitudes.

The young European who finds himself in the tropics for the first time is surrounded very often by luxuries in the shape of food, wine, conveyances, servants—luxuries to which he had not been accustomed, perhaps, in his home. At first the change, the excitement of novelty, and the high temperature act as stimulants to appetite, and the excessive loss of fluid by cutaneous transpiration creates a powerful thirst. He is made lazy by the heat; he cannot exercise during the day, and when evening comes he prefers lounging on the veranda or hanging about the club bar to walking, or riding, or games. Very likely he sits up late at night, drinking and smoking, so that in the morning he is too sleepy to ride out or take any other form of exercise. And so it comes about, what with a surcharge of aliment and alcohol, and the diminished activity of lung metabolism and excretion incident to high temperature and muscular inactivity, that a very large and unusual amount of physiological work is thrown on the liver. With this large amount of work there is a corresponding hyperæmia. This may be considered the first stage of tropical liver—hyperæmia from functional activity; up to this point it is a purely physiological condition.

Pushed a step farther, this physiological hyperæmia passes into congestion with blood stasis, and a consequent diminution of functional activity. Hyperæmia of a physiological character will be evidenced by increase of functional activity, and there will be a copious flow of bile, sometimes causing diarrhœa of a bilious character, particularly morning diarrhœa. But when the limits of physiological hyperæmia are passed, and congestion of a pathological character sets in, the consequent arrest of function will be evidenced by pale stools, perhaps diarrhœa of a watery, frothy,

fermenting character—in the last case the diarrhoea doubtless depending, in part at least, on fermentative processes set up in the contents of an alimentary canal no longer kept relatively aseptic by an adequate supply of healthy bile. Other symptoms of this condition are headache; furred tongue; scanty, high-coloured, loaded urine; a feeling of weight or fullness, or even of pain, in the region of the liver, and, probably, extension of the percussion area and other physical signs of enlargement of that organ.

Treatment.—Nature sometimes effects a cure in these cases of hepatic congestion by establishing a smart diarrhoea. In the treatment of such cases we cannot do better than to imitate Nature, and even supplement her efforts. A few doses of the sulphates, in the shape of some kind of bitter water or of Carlsbad salts,¹ generally give prompt relief. But if the subject of such attacks does not profit by experience and mend his ways, very likely his liver, in time, will become chronically hyperæmic and extremely liable to intercurrent attacks of congestion of a character more or less acute. The subjects of this type of “liver” ought to be most careful in their habits. They must not lie abed too long; they must not have cold baths; they must not take cold drinks, nor expose themselves to cold in any form; they must clothe warmly; and they must eschew alcohol in every shape. Animal food they must partake of but sparingly; they should give the preference to fowl and fish over beef and mutton. Fruit and farinaceous food may be more freely partaken of, but over-eating in every form must be avoided. Exercise should be taken at least twice a day; and, at least once in twenty-four hours, the exercise should be of such a character as to provoke perspiration.

¹ A good substitute for Carlsbad salts consists of sod. sulph. 2 parts, sod. bicarb. 1 part, sod. chloride 1 part.

CHAPTER XXVII

INFANTILE BILIARY CIRRHOSIS

THIS disease is found to be more prevalent in Hindu than in Mohammedan children. Thus, in Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces; it is more prevalent in rural districts than in towns.

Etiology—The cause of infantile biliary cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It has also been observed that it tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarks that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believes the true etiology to be in a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the foetus, overfeeding of the child when born, and the insufficient feeding of milch animals. Megaw, in India, has pointed out recently the close association between cirrhosis of the liver and bacillary dysentery. He believes the one to be the direct sequel of the other.

Pathology.—Gibbons has given an elaborate and most careful account of the pathological anatomy of this disease; he concludes that it is a peculiar

form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regards as evidence of a natural curative effort having for its object a regeneration of the liver-cells. Green-Armytage calls the disease intercellular hepatic cirrhosis.

Symptoms.—Commencing insidiously, the characteristic initial enlargement of the liver may have made considerable progress before the disease is suspected. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia, irritability of temper, thirst, and languor call attention to the child's condition. On examination the liver is found to be enormously enlarged, extending perhaps to the umbilicus or even lower. The surface of the organ is smooth; the edge, at first rounded and prominent, as the liver begins to contract becomes sharp and distinct and can be readily grasped between the fingers, the swollen organ feeling hard and resistant. The spleen may be enlarged, as in most hepatic cirrhoses. Fever of a low type sets in; the sallowness deepens into profound jaundice; the stools are clay-coloured, the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. The skin may be bronzed almost as deeply as in Addison's disease. Sooner or later, death from cholæmia ensues.

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instructions, recovery takes place in six to ten weeks. Whenever possible, the latest baby, in a family in which several cases of this disease have already occurred, should be immediately removed from the mother and artificially nursed.

Prevention.—The mother must be fed properly in the antenatal and nursing periods. When weaning occurs, the child should be fed on good cow's milk. The child should not be fed on patent foods or sweets, and 2-3 oz. of fresh fruit should be given daily; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are wanting in salts.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXVIII

LEPROSY (ELEPHANTIASIS GRÆCORUM)

Definition.—A chronic infective granulomatous disease produced by a specific bacterium, and characterized by lesions of the skin, nerves, and viscera, eventuating in local anæsthesia, ulceration, and a great variety of trophic lesions. After a long course it is almost invariably fatal.

History.—Known from ancient Chinese, Indian, and Egyptian writings, leprosy was possibly introduced into Greece between 400 and 345 B.C. In the time of Celsus—53 B.C. to A.D. 7—it was still a rare disease in Italy. By the end of the seventh century it was well known in southern Europe, and was first introduced into England about 950.

During the Middle Ages leprosy was common in Europe, so that the rulers and clergy instituted leper asylums and enacted laws for the isolation of lepers. The last British leper died in Shetland in 1798.

Leprosy still lingers in Italy, France, Spain, Germany, and Russia, as well as in Greece, Iceland, and Norway. Our modern knowledge of the disease dates from the discovery of the *Bacillus lepræ* by Hansen in 1874.

Geographical distribution.—At the present time leprosy is a disease of tropical and subtropical countries. Experience shows that the endemic area enlarges as our knowledge of the natives of uncivilized regions becomes more intimate.

In India leprosy is prevalent: in 1891 it was estimated that there were 105,000 lepers in a population of 210,000,000—a ratio of about 5 in 10,000. Recent statistics show that the highest endemic rate is in Central Africa.

Recent introduction.—The modern introduction of leprosy into virgin soil, so to speak, has taken place in the Sandwich Islands, in New Caledonia, and elsewhere. In the Sandwich Islands leprosy was noted among the aborigines for the first time in 1859, and soon spread so rapidly that by the year 1865 there were 230 known lepers in a population of 67,000. In New Caledonia leprosy was unknown until 1865; in 1888 the lepers there numbered 4,000.

Epidemiology and endemiology. *Age.*—Cases are on record of the occurrence of leprosy as early as the first and second years of

life, but are quite exceptional. Leprosy is extremely rare before the fifth or sixth year, but Rodriguez has shown that 44 per cent. of children who have lived seven to ten years with their leper parents, become infected. In the great majority of instances the disease begins between the tenth and thirtieth year. It rarely commences after 40, although it has been known to begin up to and even after 70.

Sex; occupation; social and hygienic conditions.—Apart from social conditions, as affording opportunity for contagion, sex seems to have little bearing on the liability to leprosy.

Sir Jonathan Hutchinson very sagaciously and truly remarked that leprosy is more especially a disease of semi-civilization. Savages are exempt; the highly civilized are exempt; but when the savage begins to wear clothes and live in houses he becomes subject to the disease.

Climate.—Climate can in no way be considered a cause of leprosy, which exists in all climates and in all latitudes; but it does seem to have some influence in determining, to a certain extent, the type the disease assumes. It would appear that the nodular form is more common in cold damp climates; the nerve form, in warm or dry climates. Rogers has shown that in hot, humid climates—the Belgian Congo, the Cameroons, and the French Ivory Coast, for example—the morbidity of leprosy is high; in very dry tropical areas, such as Peru and south-west Africa, it is low. The conditions favouring the spread of leprosy are: high relative humidity, close and continued contact, and type of disease—the nodular being the more infective.

Etiology.—It is now generally conceded that *B. lepræ* is the cause of leprosy, just as *B. tuberculosis* is the cause of tubercle. Authorities differ, however, as to the way in which the bacillus is acquired.

Conveyance of the lepra bacillus from man to man.—Many attempts have been made to communicate leprosy to man by inoculation; hitherto, with one questionable exception, all have failed; this was in a Sandwich Islander, who within a month suffered from leprosy neuritis. He died six years later. The experiment was vitiated by the fact that members of his family were lepers.

How acquired.—There are two principal views as to the way in which the bacillus is acquired—heredity and contagion.

Heredity.—From the fact that it tends to run in families and that in certain instances it assumes the appearance of atavism, leprosy was formerly believed to be hereditary. If this were so, how explain the striking fact, brought

out by Hansen, that of the numerous offspring of 160 Norwegian lepers who emigrated to America not one has become a leper? Although acid-fast bacilli have been found in the placenta, the evidence of the Culion settlement in the Philippines is that leprosy is not hereditary.

Contagion.—The best authorities now believe that leprosy is propagated by contagion, and only by contagion. The same unanimity of opinion does not obtain as to the particular way in which, or medium by which, the contagium is applied; but that it passes, directly or indirectly, from the infecting leper to the recipient, nearly all are agreed to regard as being practically proved. Not only may a native of a non-leper country acquire the disease on visiting a leper country, but he may also communicate the disease to others, his countrymen, on his return to his own country. There is at least one well-authenticated example of this on record. Dr. Hawtrey Benson, in 1872, showed at the Medical Society of Dublin a leper, an Irishman, who had acquired his disease in the West Indies, and conveyed it to his brother. Nodular leprosy is potentially much more infective than is the anæsthetic form.

Many similar instances of the communication of leprosy by contagion are on record, one in which a wife contracted the disease from her leper husband in England. The first symptoms of the disease appeared seven years after his death. If leprosy is proved to be communicable by contagion in one case, the probabilities are that it is so acquired in every case.

Probably intimate personal contact, and certain concurrences in the phases of the disease with special conditions in the health or physiological state of the recipient, are necessary for the successful communication and acquisition of leprosy. The simple implantation of the bacillus does not suffice; for, as already pointed out, of the many inoculations that have been made, only one has any claim to be regarded as having been successful.

Bacillus lepræ.—The lesions of leprosy are the result, direct or indirect, of the proliferation of the *B. lepræ* in the tissues. This bacillus (Fig. 83), in size, shape, and staining reactions, closely resembles that of tubercle. In length it is from half to two-thirds, and in breadth about one-sixteenth, the diameter of a blood-corpuscle. The ends of the rod—which is always straight—are in many specimens somewhat attenuated. By some authorities it is said to possess a gelatinous capsule. In common with *B. tuberculosis* and *B. smegmæ*, it retains carbol-fuchsin stains after being treated with mineral acids, though it may be distinguished by its staining more readily with cold weak solution of carbol-fuchsin, and by being decolorized more easily with dilute acids but not by alcohol; by the impossibility hitherto experienced of growing it on the usual culture media, and of successfully inoculating it into man and the lower animals; by its tendency to occur in dense clusters and in greater

numbers ; and by its very generally being found inside cells or in zoogloea masses in the lymphatic spaces.

Specimens of the bacillus can be procured readily by excising a portion of a leproma ; or they may be obtained by clamping a succulent leproma, pricking the now pallid tumour, and then collecting on a cover-glass the droplet of "leper juice," which, when spread out on the cover-glass, is fixed, stained, and decolorized as for the demonstration of tubercle bacilli. Better preparations are obtained by making with a small scalpel a minute incision into

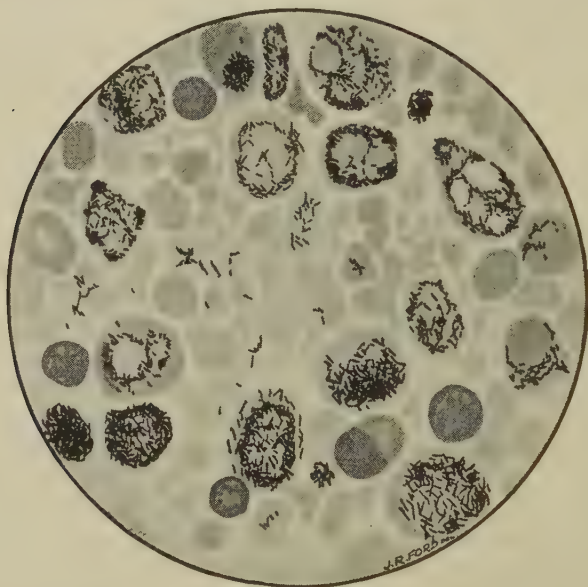


Fig. 83.—Section of spleen showing lepra cells and lepra bacilli.
× 800. (*Orig.*)

the compressed leproma, scraping some of the tissues from the under-surface of the skin, and smearing this with the juice on to the cover-glass.

The bacillus is found in all primary leprous deposits ; in the skin leproma—where it occurs in prodigious numbers ; in the meagre infiltration of the macular eruptions—where it is much more sparsely distributed ; in the early stage of leprous neuritis—where, also, it is present only in small numbers ; in the specific lesions of the liver, spleen, testes, lymphatic glands, and lungs. In the blood-vessels it has been found in the endothelium and,

occasionally, free in the blood or enclosed in leucocytes. It is abundant in the purulent discharges from the nose, from ulcerating lepromata, or other forms of primary leprous infiltration. It has very rarely been found in the spinal cord or in the lungs. In nodular leprosy bacilli have been demonstrated in numbers in what appears to be apparently normal skin. One modern view is that *B. lepræ* is a streptothrix like the actinomyces, or, according to some, that like the tubercle bacillus it is pleomorphic to a high degree, and that at a certain stage of growth and under certain conditions the mycelia break up into short rods, many of which are now acid-fast. There is great discrepancy of opinion among bacteriologists on the subject, each observer having his special lepra germ grown on his special culture medium; this germ he regards as the only true one, conforming, it is claimed, to the proper agglutination and complement-deviation tests, and its products possessing a therapeutic value comparable to that of tuberculin, and giving rise to a local and a general reaction when injected into lepers.

“*Rat leprosy.*”—The discovery that rats (5 per cent. in Paris) are subject to a disease clinically resembling human leprosy was at first thought to shed some light on human leprosy, seeing that the lesions of rat leprosy, as it is called, are intimately associated with an acid-fast bacillus resembling that of human leprosy, and that the disease is communicable to other rats by association.

Pathology.—The young leproma presents a smooth, white, glistening section, but when older becomes browner. The specific lesion of leprosy differs from that of tubercle inasmuch as the former is well supplied with blood-vessels, contains no true giant-cells, and never undergoes caseation. If hardened, cut, and stained, the leproma is found to consist chiefly of small round cells about the size of a leucocyte, epithelioid cells, and fusiform cells, which are arranged for the most part in groups, generally around or near blood-vessels; the majority of these cells contain bacilli—some having only a few, while others are crammed with the organisms. Isolated bacilli are also found scattered through the preparation, apparently free in the lymph-spaces.

In addition to the bacilli-bearing cells, and increasing in number with the age of the lesion, a number of brown granular bodies, larger and smaller, named “globi,” are to be seen; these are thought to be cells in which the bacilli have perished and become granular. In old maculæ, as well as in very old lepromata, the bacilli may be hard to find or entirely absent. In the anæsthetic maculæ the terminal nerve-fibres are degenerated. As the fusiform thickening of the larger nerve-trunks in nerve leprosy is a secondary inflammation, bacilli may not always be found, although, at the very commencement of the nerve disease, bacilli are present both in the cells and lying free between the axis-cylinders. In time the affected nerves become mere fibrous cords destitute of nerve tubules.

The anatomy and the histology of the various trophic lesions are such as are found in other examples of destructive neuritis, and are in no way peculiar to leprosy.

In nodular leprosy the liver and spleen are the seat, in many instances, of a peculiar infiltration which, in well-marked examples, may be visible to the naked eye. Fine yellowish-white dots and streaks, consisting of new growth and bacilli, are seen to occur in the acini.

Sometimes in nodular leprosy the testes atrophy and undergo fibrotic changes, bacilli and globi being found both in and around the tubules, free and in cells. In all forms of leprosy the lymphatic glands draining parts in which the leprous deposit is present are affected; they are swollen and hard, and on section the gland tissue is seen to have a yellowish tinge from an infiltration which contains numerous bacilli and globi.

Albuminoid disease of the alimentary canal, liver, and spleen, and nephritis, occur in a large proportion of the cases of nodular leprosy.

Symptoms.—Although *B. lepræ* is the cause of all leprosy, the clinical manifestations of its presence are far from being identical in every case; indeed, they are almost as varied as are those of syphilis or of tubercle. As a matter of fact, in its earlier stages leprosy is far from being always, or even generally, a striking disease. Sometimes, it is true, it is suddenly and frankly declared from the outset, and progresses rapidly; but in the vast majority of cases the early lesions are trifling and are apt to be misinterpreted or overlooked, and years elapse before serious mutilation or deformity is produced.

To facilitate description, it seems advisable to divide the evolution of leprosy into stages, premising, however, that the division proposed is in great measure an artificial one.

1. *Primary infection.*—Seeing that leprosy is caused by a specific bacillus, there must have been a time in the history of every leper when the infection entered the body, but there is no local lesion to mark the spot. Probably it is inoculated on to some accidental breach of surface, or, at any rate, intimate contact with a leper seems to be essential.

The bacillus is found in the nasal mucus in the majority of early cases of leprosy. It is therefore considered by some that the initial lesion of the disease is a specific ulceration of the cartilaginous septum of the nose which may give rise to epistaxis.

2. *The period of incubation.*—This is generally, possibly always, long, and has to be reckoned usually in years—two or three at least, it may be ten. Extreme cases in which the period varied between fourteen and forty years have been described (Norman Walker). On the other hand, cases are on record in which the incubation period was set down at three months, or even at a few weeks.



EARLY MACULAR RASH OF LEPROSY.

(By permission of London School of Hygiene and Tropical Medicine.)

Note distribution along course of ulnar nerve.

3. *Prodromata*.—Fever of greater or less intensity and occurring more or less frequently is, almost invariably, a feature of the prodromal stage of leprosy. Febrile attacks with weakness and drowsiness may recur off and on during one or two years—and may be mistaken for malaria. Dyspeptic troubles, associated with diarrhoea in some cases, with constipation in others, are also common. Epistaxis and dryness of the nostrils have been noted. Headache; vertigo; perversions of sensations—such as localized pruritus, hyperæsthesia, “pins and needles.” general aching, rheumatic-like pains in loins, back, and elsewhere—all or any of these may herald the explosion of unequivocal leprosy.

The liability in many instances to excessive sweating, which comes on without apparent or on very slight provocation, is another curious feature of early leprosy. As pointed out by Leloir, this hyperidrosis may be general, or it may be confined to particular parts, most often the trunk, the limbs being unaffected or even being the subject of anidrosis.

4. *The primary exanthem*.—In a considerable proportion of cases, after a longer or shorter period of indifferent health, sometimes preluded by an outburst, more severe than usual, of fever and other prodromal phenomena, an eruption appears on the skin. (Plate XXVI.)

The spots may be no larger than a millet-seed, or they may occupy surfaces many inches in diameter; they may be numerous, or there may be only two or three; in some cases they may be pigmented from the outset; or they may be mere vitiliginous patches; or all three forms of maculæ may occur in the same individual—erythematous, pigmented, and vitiliginous. In not a few lepers, what in the first instance was an erythematous patch may in time become pigmented, or it may become pale; in the latter case the loss of pigment is usually associated with a certain degree of atrophy of the cutis. In certain instances the eruption of the various forms of maculæ may be preceded by local paræsthesiæ, such as a sense of burning, tingling, pricking, and so forth.

A striking feature of this and of all leprous eruptions is the loss of the hair in the affected areas. Another striking circumstance is the fact that the most hairy part of the body, the scalp, is never or very rarely affected either with leprous eruptions or with leprous alopecia. As the face, particularly the superciliary region, is prone to all forms of leprous eruption, depilation of the eyebrows is a very usual, very early, and very characteristic phenomenon. The beard, too, is apt to be patchy, particularly in nodular leprosy.

The most frequent seats of the primary macular eruption are the face, especially the superciliary region, the nose, cheeks, and ears; the extensor surfaces of the limbs; the backs of the hands; the back, buttocks, abdomen, and chest. The palms of the hands and the soles of the feet are rarely if ever attacked. At this stage of the disease the mucous membranes are very seldom affected.

5. *The period of specific deposit.*—Sooner or later, however, another stage is entered upon, a stage characterized by the deposit or, rather, growth of a tissue possessing well-marked specific characters. This deposit occurs either in the skin, or in the continuity of the peripheral nerve-trunks, or in both. If in the first situation, nodular or, as it is sometimes called, tubercular leprosy is the result; if in the second, we have nerve or anæsthetic leprosy; if in both of these situations, then what is known as “mixed leprosy” is produced.

NODULAR LEPROSY.—This form of leprosy often appears without a well-marked preliminary macular stage, being ushered in, after a longer or shorter prodromal stage, by a smart attack of fever and the rapid development, on the face or elsewhere, of the specific lesion.

The essential element in nodular leprosy is the leproma. The dimensions, the combinations, the situations, the growth, and the decay of this give rise to the more manifest symptoms of the earlier stages, at all events, of the disease. The leproma is formed by infiltration of the deeper layers of the derma with what at first is a small-celled, somewhat dense neoplasm. In size it ranges from the dimensions of a split pea, or of a bean, to a great plaque many inches across. In colour it differs according to its age and condition, and according to the natural hue of the skin of the leper; it varies from red to dirty pink in the earlier and congestive active stage, to dark brown or dirty yellow in the later stages. It is generally—though not always, especially at first—anæsthetic to some degree, if not absolutely so; it is devoid of hair, usually somewhat greasy-looking and, perhaps, stippled with gaping sebaceous follicles. Isolated lepromata are generally round or oval; when contiguous they may coalesce, forming patches of irregular outline.

When many lepromata run together, or are closely set, the growth causes the natural folds of the skin to be exaggerated; great disfigurement, especially of the face, may ensue (Fig. 84). The appearance becomes repulsive and “leonine.”

Nodules may appear in greater or less profusion on the

limbs and body; favourite sites being the backs of the hands, the external surfaces of the arms, the wrists, the thighs, and the groins.

From time to time, and at longer or shorter intervals, fresh lepromata appear, their formation generally concurring with an outburst of fever. The normal and usual fate of the nodule is either first to soften in the centre and then to be absorbed, leaving a smooth circular patch of scar tissue; or, after softening, to ulcerate and discharge a sticky, yellowish pus.

When the septum of the nose is affected, the cartilage breaks

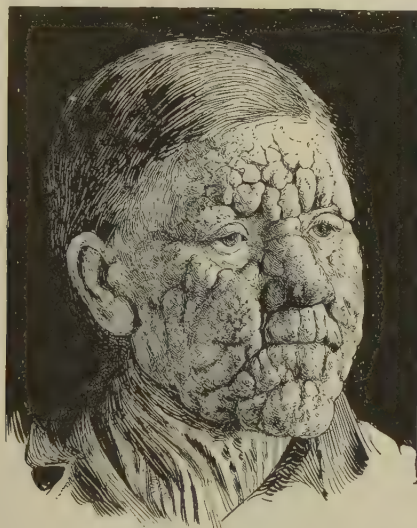


Fig. 84.—Nodular leprosy. (*After Leloir.*)

down, the tip of the organ becomes depressed, and a stinking discharge escapes from the nostrils.

The eyes, also, are sooner or later attacked, lepromatous growth spreading from the conjunctiva on to the cornea or into the anterior chamber, or originating in the iris or ciliary body. Ultimately these organs also are destroyed.

Fortunately, in a large proportion of cases the leper is mercifully carried off by phthisis, pneumonia, or some intercurrent affection at an earlier period, and before his disease can be said to have run its full course.

NERVE LEPROSY.—Just as in nodular leprosy, in nerve leprosy the prodromal and macular stages may be severe, or slight, or

altogether absent. Usually, however, in nerve leprosy much more frequently than in nodular leprosy, the ulterior and more distinctive lesions are preluded by a long and well-marked macular stage, during which large areas of skin are occupied by erythematous



Fig. 85.—Nerve leprosy. (After Leloir.)

(Fig. 85), by pigmented, or by vitiliginous patches. The ringed form of eruption is a very usual one; a red, congested, slightly elevated and, perhaps hyperæsthetic border enclosing a larger or smaller area of pale, anæsthetic, non-sweating integument—the



ANÆSTHETIC LEPROSY.

Showing macular rash around elbow-joint. Note atrophic appearance of skin.

PLATE XXVII

whole resembling somewhat one of those extensive body-ringworms so common in natives of hot, damp climates, and for which these rings are sometimes mistaken. (Plate XXVII.)

A frequent and very distinctive symptom of this type of the disease, occurring often about this time, is the sudden appearance of bullæ (*pemphigus leprosus*) of various sizes—one or more or a series of them—on the hands, feet, knees, backs of thighs, or elsewhere. After a few days they rupture, exposing a reddish surface which presently crusts over, exfoliates, and finally turns into a pale, perhaps anæsthetic spot with a sharply defined pigmented border. More rarely the site of the bulla ulcerates.

A time comes when evidence of profound implication of the nervous system, in the shape of severe neuralgic pains, formication, hyperæsthesia, or anæsthesia, becomes more accentuated. The lymphatic glands enlarge, and there is often considerable fever with general distress. But, whether the skin lesions increase or retrogress, evidences of profound implication of the peripheral nervous system now distinctly show themselves; the neuralgic pains still further increase, and hyperæsthesia, anæsthesia, and various paræsthesiæ, along with trophic changes in skin, muscle, and bone, the results of nerve destruction, become the dominating elements in the case.

If at this stage the ulnar nerve where it passes round the internal condyle of the humerus be examined, generally it will be found to be the seat of a fusiform swelling, perhaps as thick as the little finger. Other nerves, such as the anterior tibial, the peroneal, more rarely the median, radial, brachial, and cervical nerves, especially where they pass over a bone and lie close under the skin, can be felt to be similarly swollen. Occasionally even the smaller nerves, where superficial, can also be detected hard and cord-like. At first these thickened nerves are tender on pressure, and the parts they supply may be the seats of hyperæsthesia and acute neuralgia. By degrees the great thickening of the nerve-trunks decreases somewhat, the hyperæsthesia and neuralgia subside, and anæsthesia, paresis, muscular atrophy, and other trophic changes take their place. Another and sometimes a very striking fact in nerve leprosy is the symmetry observed in the distribution of some of the anæsthetic areas. McIlhenny has pointed out that the temperature of anæsthetic digits is from two to three degrees lower than normal.

Step by step with the progress of the anæsthesia, atrophy of the subjacent muscles supplied by the thickened nerves proceeds. Along with the atrophy there is a corresponding distortion and

a corresponding loss of power. Thus the forearm wastes, the grasp is weakened, the thenar and hypothenar eminences and the interossei melt away, and the *main-en-griffe* or some such deformity is gradually produced (Fig. 86).

In the affected nerve areas all the muscles are not simultaneously or equally attacked, so that, especially in the face, curious distortions may ensue. Owing to muscular atrophy, the eyes, after a time, cannot be closed; the upper lid droops, the lower lid becomes everted, and the eye itself may become fixed. (Fig. 87.) At first, owing to exposure of the organ, there is lacrymation; but by and by the secretion of tears dries up, the congested conjunctiva becomes cornified, the cornea ulcerates or turns leucomatous, and in the end sight is entirely lost. Ulceration often occurs in the mucous membrane of the nose, the septum being destroyed as



Fig. 86.—Nerve leprosy : *main-en-griffe*. (After Leloir.)

in the nodular form; the tip of the nose may then fall down or be entirely lost. The lips, too, may become paralysed, thereby interfering with articulation and permitting saliva to dribble from the mouth in a constant stream. Changes, too, occur in the mucous membrane.

In time the skin of anæsthetic patches on the limbs tends to atrophy; it loses its glands and hairs, and, in the end, may become so thinned and tense that it actually bursts into long cracks. The nails are not generally shed, but they become rough, or thinned, or atrophied into minute, hook-like appendages.

Ulcers form over exposed parts of the hands and feet. They may penetrate and disorganize the joints, and thus often cause fingers and toes to drop off, one after another. Or, perhaps, an abscess forms around a phalanx, destroys the periosteum, and ultimately leads to loss of the bone. In any of these ways the fingers and toes are distorted or destroyed. It is no unusual thing to see on a leper's hand a finger in which one or more of the phalanges

have been thus got rid of without destruction of the fleshy part, or with only a general shrinking.

Perforating ulcer of the sole of the foot, usually under the ball of the great toe or the heel, is a very common lesion in nerve leprosy.

On the whole, the advance of this form of leprosy is much slower than that of the nodular variety.



Fig. 87.—Leprotic infiltration causing paresis of facial muscles and paralysis of orbicularis palpebrarum. (*Orig.*)

Diagnosis.—The touchstone in all doubtful cases is the presence or absence of anæsthesia in some skin lesion or in some skin area. Anæsthesia is rarely absent in leprosy; generally in the implicated spots it is complete, or nearly so. It should be particularly sought for towards the centre of maculæ, in the pale patches left after the fading of former maculæ, in the hands and feet, and in nodules of some standing. In no other skin disease is definite anæsthesia a symptom.

It is usually in the diagnosis of incipient cases that difficulty is liable to arise. Early deposits are frequently seen or felt on the forehead, and there is often a tell-tale thickening situated in or around the naso-labial fold. Powell has pointed out that in the majority of cases of leprosy in men hypertrophy of the nipple takes place (Fig. 88).



Fig. 88.—Leprosy, showing hypertrophied nipples. (Orig.)

Vitiligo or *leucodermia*—sometimes called white leprosy, and by the vulgar very generally regarded as true leprosy—bears a certain resemblance to the pale postmacular patches referred to; not to mention other features, the absence of anæsthesia in leucodermia at once settles diagnosis.

The sensory and trophic lesions of *syringomyelia* might be

mistaken for nerve leprosy, but the general history of the case, the history or presence in leprosy of macular eruption, of thickened nerve-trunks, and of enlarged lymphatic glands, and the absence of these phenomena in syringomyelia, are mostly sufficient to establish a diagnosis.

The occurrence of an acid-fast bacillus in the sputum of a patient coming from a country in which leprosy is common should be regarded with suspicion, and its true nature tested by injection of the sputum into the guinea-pig, as tubercular infection commonly coexists in lepers.

It is hardly necessary to point out the diagnostic marks of leprosy as against syphilis,¹ erythema multiforme, erythema nodosum, acrodynia (a disease allied to ergotism), trypanosomiasis, lupus vulgaris, lupus erythematosus, psoriasis, eczema, lichen planus, cheloid, body-ringworm, erythrasma, pityriasis versicolor, pellagra, and filarial elephantiasis. Mistakes can scarcely be made unless from carelessness, or by someone completely ignorant of the nature, history, and symptoms of these diseases.

When confirmation of a clinical diagnosis is required a portion of tissue may be excised for microscopic section, or the bacilli may be demonstrated in the nasal mucus or in serous fluid expressed from a nodule. By raising a blister on a nodule, or on an anæsthetic patch by means of carbon-dioxide snow, a quantity of serum may be obtained in which on centrifugation leprosy bacilli may be demonstrated.

Prognosis.—Complete recovery is an event so rare in leprosy that, though it may be hoped for, it must not be expected. Recovery from the actual disease itself—that is, in the sense that fresh leprous infiltration may cease to occur, and old infiltration may be absorbed, and that the bacilli may die out—is perhaps the rule in nerve leprosy; but the effects of the leprous process are generally permanent, the trophic lesions resulting from nerve destruction being irremediable. Such cases may live, however, for many years—thirty or forty—and die of some other disease, though in an appreciable proportion, according to Muir, the disease becomes arrested.

Nodular leprosy is usually a much more acute disease than

¹ Unfortunately the Wassermann reaction cannot always be relied upon as a guide in differential diagnosis. Lloyd, Muir, and Mitra report that 63 per cent. of nodular cases and 27 per cent. of anæsthetic cases in adults give positive Wassermann reactions: at least three quarters of these positive reactions are due to coexisting syphilis as evidenced by the effect of antisyphilitic treatment. There remains a small residue of cases in which the positive reaction appears to be due to leprosy alone, especially in the nodular form.

nerve leprosy, sapping the strength and general health much more effectually and more quickly. It rarely runs its full course, death being brought about by some intercurrent disease, such as, and especially, phthisis, or nephritis, albuminoid degeneration of the alimentary tract, dysentery, stenosis of the larynx, or pneumonia. It may even prove fatal as a sort of "galloping" leprosy within a year of its first declaring itself.

Treatment.—Scrupulous and systematic attention to personal and domestic hygiene and cleanliness; frequent bathing and the free use of soap; frequent changes of underclothing; good food; fresh air; light work; the avoidance of overstrain, of fatigue, and of exposure to bad weather—these things are all of prime importance in the treatment of leprosy, and should be insisted on. It has been found that most lepers on being placed in favourable hygienic conditions improve for a time, and that in a small proportion of cases the disease by these means may sometimes be actually arrested. Europeans who have contracted leprosy in the tropics almost invariably undergo temporary improvement on return to the more bracing climate and more nutritious diet of their native land.

One is very apt to be deceived in estimating the value of a drug in leprosy. The leper applies for treatment generally during, or soon after, one of the periodical exacerbations of the disease, and when the nodules and other eruptions are active and well pronounced. In the natural course of events, and without treatment of any description, especially if the patient be placed under favourable hygienic conditions, these acute manifestations tend to become quiescent, and the disease temporarily to ameliorate; this temporary improvement is then apt to be ascribed to the drug.

Chaulmoogra oil (*Oleum gynocardium*, obtained from the seeds of *Taraktogenos kurzii* in Burma and Assam; *Hydnocarpus wightiana* in Southern India; and *H. anthelmintica* in Siam and China), in doses of from 2 to 10 up to 40 drops or more, according to tolerance, three times a day, together with inunction of the same drug mixed with some oil, is a favourite remedy with English practitioners. Such lepers as can assimilate large doses of this drug appear to derive benefit. The oil of *Hydnocarpus wightiana* is much preferred by many observers, notably Rogers, to the former. It has the further advantage of being more easily procurable, being grown in gardens and accessible places all over the south of India, so that the seeds can be obtained fresh.

Ethyl esters of chaulmoogra.—Originally Messrs. Bayer & Co.

produced an ethyl ester of chaulmoogra which they named Anti-leprol; this is put up in capsules of 15 gr. each and given intramuscularly or by the mouth twice weekly, and in gradually increasing doses. Later, Dean & McDonald, in Honolulu, believing chaulmoogra oil to be inabsorbable when injected as such into the tissues, have produced a similar preparation suitable for intramuscular injection.

The standard preparation now used for injection consists of the ethyl esters of the entire fatty acids of the whole oil, with 2 per cent. of chemically-combined iodine (this preparation is sold as *Moogrol*—Burroughs Wellcome). The initial dosage is 1 c.c. given intramuscularly, and this is increased by the same amount at every second or third injection, until 5 or 6 c.c. are reached, depending upon the age and weight of the patient. At the same time a ricinoleate containing 2.5 per cent. of iodine in chemical combination (sold as *Iodicin*—Burroughs Wellcome) is given, either in capsules or in tabloids, by the mouth. The dosage should be 0.25 grm. per 100 lb. of the patient's weight, taken thrice daily, and it is recommended that the dose should be increased every two weeks until a maximum of 1 grm. per 100 lb. of weight is reached.

Travers in the Malay States, has recorded good results from the Chinese treatment of leprosy by oral administration of a powder consisting of *Hydnocarpus anthelmintica* seed, 3 parts; *Cannabis indica* seed, 1 part; given in half-drachm doses twice daily after food, and proportionately less for children. If febrile reactions occur the treatment is stopped for a time. The treatment is very popular, occupies little time, and the cost is minimal.

In 1890 Roux pointed out that gynocardic acid and gynocardates of soda and magnesia could be obtained from chaulmoogra, and were better borne. Heiser first suggested the method of subcutaneous injection, and since then Rogers has obtained what he believes to be encouraging results from the intravenous injection of *sodium gynocardate*¹ in doses of $\frac{1}{10}$ to $\frac{4}{5}$ gr. in 3-per-cent. sterilized solution. A definite local reaction in a proportion of cases, sometimes with fever, follows the injection, which is believed to indicate destruction of the organisms within the lepromata. Thrombosis of the vein and phlebitis are apt to occur as a result of continued intravenous injections. It is important to inject gynocardates free from palmitic acid, so as to avoid pain and swelling. For intramuscular dosage a minimal dose of 2 c.c. (4 gr.) of sodium

¹ The drug, put up in proper doses in ampoules, can be obtained from Messrs. Smith, Stanistreet & Co. Two salts of gynocardic acid are present—sodium gynocardate and sodium hydnocarpate.

gynocardate solution is recommended, the maximum being 12 c.c., or 24 gr., given twice weekly.

Sodium hydnocarpate in a 3-per-cent. solution is given intramuscularly or subcutaneously, twice weekly in doses commencing with 0·5 c.c. and increased by the same amount at each dose up to 5·0 c.c. or more.

Latterly *sodium morrhuate* (1 c.c.) has been combined with the gynocardate.

Two other modern methods of injecting chaulmoogra must be referred to. The mixture known as E.C.C.O. consists of the ethyl ester of *Hydnocarpus wightiana*, creosote, camphor, and olive oil, given hypodermically in $\frac{1}{2}$ -c.c. doses, intravenously in $\frac{1}{4}$ -c.c. doses, the maximum being 7 $\frac{1}{2}$ c.c. The second form, C.E.I., is a mixture of

Chaulmoogra	50 parts.
Sulphuric ether	.	.	.	50 „
Iodine	.	.	.	0·1 part.

The latter preparation should be increased up to the point of tolerance. The initial doses, given intravenously—daily injections—are 0·25 c.c., increased very gradually till 1 c.c. is reached. C.E.I. produces a considerable reaction; it may be varied with injections of E.C.C.O.

A recent advance is the use of an improved sodium hydnocarpate prepared from the lower-melting-point salts of *Hydnocarpus anthelmintica* and now known as *Alepole*. A 3-per-cent. solution is quite painless when given as a subcutaneous or intramuscular injection, and a 1-per-cent. solution can be injected repeatedly intravenously without causing thrombosis.

Potassium iodide.—Muir in Calcutta has recorded good results with large doses of potassium iodide in advanced cases. It is given twice weekly, gradually increasing the dose till the maximum is reached, so that 120 or even 240 grains are given in one dose.

Ephedrine.—An alkaloid obtained from the drug Ma Huang, in doses of 2 gr., given in hard gelatin capsules by the mouth, is recommended by Muir for the alleviation of the distressing nerve pains of leprosy.

Antimony and its salts have recently received a trial. It may be given in the colloidal form as an intramuscular injection, known as Oscol stibium, 1 c.c. being given at intervals of three days; or intravenously in the form of stibacetin, 0·2 grm. twice weekly. According to Muir, intravenous antimony-tartrate has the effect of controlling prolonged febrile reactions.

Carbon-dioxide snow.—Some reference must be made to what is known as Paldrock's method of treatment in Dorpat. This is

the application of CO₂ snow not only to the leprous tissue in contact with it, but a great many nodules in the vicinity; but this general effect only lasts a short time.

Surgical measures.—When leprous nodules spread on to the cornea and threaten to interfere with the line of vision, Brockmann has shown that the extension of the leproma may be arrested by division of the cornea on the pupillary side of the lesion; it is found that the bacilli do not traverse the cicatrix. Tarsorrhaphy for ectropion of the lower lid, iridectomy for iritis or synechiæ, tracheotomy for laryngeal stenosis, and necrotomy for bone disease, may sometimes have to be performed. Horder strongly recommends amputation for perforating or other forms of leg ulceration, as the general health is much improved by the removal of such sources of sepsis. The existence of leprosy does not materially interfere with the success of surgical operations. Manson once removed an enormous elephantiasis of the scrotum from a confirmed leper; the presence of the leprosy did not prevent sound healing of the extensive operation wound, the man making a good recovery from the operation.

Deformities may be corrected and functions restored by massage, baths and active exercise. Those with marked contractures, in which motion is absent, can be treated by deep therapy light, massage, passive extension, splinting and bandaging. Necrosis can be treated by ultraviolet-rays; rarefying osteitis by the same means, massage, and exercise. Patients with nerve lesions can be treated by diathermy.

If only one tubercle or one limited lepromacule is present, and there have been no constitutional signs of a general invasion, it is advisable to excise freely the affected spot.

Other symptoms have to be treated as they arise; laryngeal affections may require insufflation of cocaine. Leprotic iritis may be extremely difficult to treat, and often atropine drops are of little avail. In these cases hyoscine, 1 gr. to $\frac{1}{2}$ oz. of water, may be used in the form of drops; it usually gives relief. For the offensive nasal discharge the following nasal lotion will be found useful:

Ry Sodii chlor.	gr. xxii.
Sodii bicarb.	gr. xxii.
Pot. chlor.	$\frac{3}{4}$ ii.
Calcii phosph.	$\frac{3}{4}$ i.

$\frac{1}{2}$ oz. to be used with $\frac{1}{2}$ -pint of warm water as a nasal douche.

Protein-shock therapy.—The favourable results produced by febrile reactions in leprosy have led various observers to try intra-

venous and subcutaneous injections of various organisms. Row, in Bombay, has recorded improvement after weekly subcutaneous injection of autolysed cultures of tubercle bacilli, washed free of fatty substance by petrol ether. Hasson has claimed remarkable results in nodular leprosy from intravenous injections of dead leprosy bacilli obtained from leprotic lesions and killed cultures of *Bacillus pyocyaneus*. A great febrile reaction is thereby produced; in order to obtain improvement, ten or more of these injections are necessary. The Editor has seen equally good results follow the intravenous injection of milk, or mixed typhoid and paratyphoid vaccine in graduated doses, and he believes that distinct benefit accrues from what is, in effect, "protein-shock" treatment. At any rate, further trial on these lines is advisable. Remarkable and almost immediate improvement in chronic cases of leprosy have been reported by Dyce Sharp in the Cameroons from this treatment.

The great difficulty in assessing the value to be attributed to any particular line of treatment, lies in the fact that leprosy in some cases becomes arrested without any special treatment. This is specially to be noted immediately on moving patients, previously living in squalor and poverty, in which conditions the disease has made headway, to other surroundings where they are better fed and housed.

It is most important that coexisting syphilis should be recognized and energetically treated with salvarsan and potassium iodide. In such cases rapid improvement in the general condition of the patient ensues, as well as in his leprosy.

Prophylaxis.—The leper must be regarded as a source of danger and, *qua* leprosy, the only source of danger to any community he may live amongst. Therefore a sure and the most effectual way of suppressing the disease is the thorough isolation of existing lepers. There are many difficulties, however, especially in such countries as India, in giving practical expression to what appears to be a perfectly logical conclusion—difficulties springing from the rights of the individual, finance difficulties, difficulties arising from concealment or incorrect diagnosis, as well as from the continued introduction of fresh cases from without.

As an instance of the possibilities open to segregation, if carried out on thoroughly practical scientific and humanitarian lines, the Culion Island Leper Colony, in the Philippines, organized and developed under Dr. Victor Heiser, may be cited. On the island is situated a town, with laundry, theatre, and schools complete. When segregation of lepers was enacted, it was found that little

compulsion was necessary, owing to the obvious advantages offered to the sufferers. Some 8,000 lepers were segregated, and at the end of ten years the number had been reduced to 3,000 by natural processes and the nearly complete cessation of new infections. Such a rapid reduction within one decade cannot be explained on any other grounds than the success of the measures adopted in removing the sources of infection.

Lepers ought not to be allowed to beg in the streets—as is often the case in Eastern cities—to keep shops, or handle food or clothes intended for sale, to wander about the country as pedlars or mendicants, to hire themselves out as servants or prostitutes, or to frequent fairs and public places. A child born of a leper should at once be removed from the diseased parent and, if necessary, cared for at the public expense.

CHAPTER XXIX

YAWS (FRAMBÆSIA)

Synonyms.—Pian ; Frambœsia ; Boubas (Brazil) ; Coko (Fiji) ; Parangi ¹ (Ceylon) ; Dube (Gold Coast) ; Purru (Malaya).

Definition.—Yaws is a contagious inoculable disease, characterized by an indefinite incubation period, and followed usually by fever, by rheumatic-like pains, and by the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it is mostly protective against a second attack. The disease is caused by *Treponema pertenue*, and is controlled by salvarsan and certain bismuth salts.

Geographical distribution.—Yaws is common in tropical Africa, the West Indies, Ceylon, the Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable to be attacked. Possibly yaws was originally introduced into America and the West Indies by the negro slaves. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared from Guiana and Barbados, where it was previously extremely rife, in recent years.

Epidemiology and endemiology. *Contagion and heredity.*—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour its occurrence. Simple skin-contact does not suffice ; a breach of surface is necessary. Probably the virus is often conveyed by insect-bites, or by insects acting as go-betweens and carrying it from a yaws sore to an ordinary abrasion or ulcer. Thus the disease frequently commences in a pre-existing ulcer. Cases are prone to originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts in which the latter had resided. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an

¹ This word means "foreigner," a term applied by the natives to the European invaders of Ceylon.

existing case. In some countries yaws, as in Ceylon, is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws unless the virus be first introduced directly through a breach of surface after birth. It is not conveyed by the milk; nor does a suckling suffering from yaws necessarily infect its nurse.

Although two-thirds of the cases in the West Indies and Ceylon occur before puberty, no age is exempt. Three males appear to be infected to every one female. Neither race nor occupation has any manifest influence. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole the negro and negrito stock is specially liable to be severely attacked by yaws.

Etiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—*Treponema pertenue* (*T. pallidulum*)—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the indian-ink method; better still, the living parasites may be detected in fresh undried films by dark-ground illumination. A fully developed yaw is unsuitable because, in consequence of its having been exposed to external sources of contamination, a variety of organisms will be present and may confuse the observer. Opinions differ with regard to the exact morphology of *T. pertenue*, but later observers, including Dobell, have been unable to distinguish any structural differences between this spirochæte and *T. pallidum* of syphilis (Fig. 215, 5, p. 709).

T. pertenue has been found in the spleen, lymphatic glands, and bone-marrow; doubtless it occurs in the blood. It is inoculable into monkeys and rabbits; in the former, especially in the orang-outang, it gives rise to lesions similar to those met with in the human subject.

Cultivation of *T. pertenue* has been successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. To succeed in the cultivation of these spirochætes, strict anaërobiosis is necessary.

Pathology.—No visceral changes have been found peculiar to yaws. An important point of contrast in the morbid anatomy

of yaws and of syphilis is the absence of endarteritis in the former and its frequency in the latter.

Symptoms.—As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.

PRIMARY LESION (*madre buba* or “mother yaw”).—According to Sellards the *incubation period* in experimentally-inoculated yaws in man is three-and-a-half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma or a papule at the site of inoculation 1–7 cm. in diameter, and is known as the “frambœsoma.” It may develop at the site of some old skin lesion. It is ordinarily extragenital, and may be situated on any part of the body. It may occur on the buttock, thigh, knee, leg, arm, or breast. The lower part of the leg is the site of predilection; the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow’s large series the genitalia were the seat of the primary lesion in 1 per cent. only. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying their children who are infected with the disease. The primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.

The lesion on becoming larger becomes covered with a yellowish secretion or scab. It is at this stage known as the “mother or master yaw,” the “mama pian” of the French.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible and are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 103° F.), persistent headache, pains—worse at night—in the long bones, joints, and loins, and sometimes gastric disturbance and diarrhœa, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption appears.

SECONDARY STAGE.—This is ushered in by a fine, light-coloured, furfuraceous desquamation. The skin becomes harsh and dry,

loses its natural gloss, and here and there the patches of desquamation (best appreciated with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and giving rise to an appearance as if the entire skin had been dusted over with flour. On the other hand, this furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white marks, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin occurs not only in the early stages of yaws, but may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. This condition has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 89).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—*frambæsia* (or *raspberry*)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half-a-crown, and, according to Spittel, they commence around the primary sore ("mother and daughter yaw"). The itching produced by these sores is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar, or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules (Fig. 90) occur in groups, the larger appearing to be surrounded by a group of satellites, which has given rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these lesions in symmetrical fashion whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region; in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters just inside the nostril. Several of the groups may coalesce to cover a large surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over their summits and splits in radiating lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair-

follicle, consisting of a cheesy-looking substance, which cannot be wiped away unless undue force is used.

The papule, having arrived at this stage, may either cease to grow, the apex becoming depressed, or may go on to the formation



Fig. 89.—Secondary yaws in a Malay boy. (W. E. Le Gros Clarke.)

of the typical yaw. In the latter case the lesion gradually grows into a rounded excrecence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more

flattened or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and en-



Fig. 90.—Secondary rash of yaws. (*By permission of Dr. Sambon.*)

crusted dirt. Deprived of its crust, the little swelling is seen to be red in colour, generally smooth and rounded on the surface, and oozes pale yellowish serum, in which spirochætes may be demonstrated; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming

with the organisms. According to size, it stands out anything from $\frac{1}{8}$ to $\frac{3}{4}$ in. above the surrounding healthy skin. Pus, unless as a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called “ringworm yaws.”

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing at the site of the former fungating mass a slightly thickened spot of fairly sound skin, which, though pale at first, may subsequently become hyperpigmented.

Histologically, the individual yaw consists of hyperplasia of the true epidermis and formation of granulation tissue; giant cells may be present.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as “acuminate papules.” These are symmetrically distributed over the back, shoulders, arms, elbows, and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the appearance of the eruption, as in secondary syphilis, there may be a uniform, painless enlargement of the lymphatic glands, in the aspirated lymph of which the specific micro-organism may be demonstrated. When the lesions subside, pigmented spots remain as in secondary syphilis, and are specially noticeable on the palms of the hands.

The serum of patients in the secondary stage gives a marked positive Wassermann reaction, and thus makes the differential diagnosis from syphilis, by that means alone, impossible.

TERTIARY STAGE.—It sometimes happens that the tumours, in place of becoming absorbed, break down and ulcerate, the ulceration, however, which may last for years, being confined to the yaw itself. In other instances ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatricial contractions. Such ulcerations occur in about 8 per cent. of cases and may, or may not, be encrusted. With the development of the deeper and wider forms of ulceration the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be not infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may

take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. A multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 91.)



Fig. 91.—Tertiary yaws. Onychia of fingers.
(W. E. Le Gros Clarke.)

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot, in consequence of being bound down by the dense and thick epidermis, it causes much suffering. Spreading laterally under the thick, leathery, and unyielding epidermis, it may attain a large size. After a time the epidermis over the growth gives way,

splitting up in a radiating fashion (Fig. 92). Pressure being thus removed, the yaw fungates, and suffering diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for *T. pertenue* is formed. A



Fig. 92.—Foot yaws, or "crab yaws." (Dr. J. G. Reed)

condition known as "clavus" in Dominica results from the healing of these granulomata; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. A similar condition of pitting occurs on the palms of the hands.

Gangosa, or destructive ulcerous rhino-pharyngitis (Fig. 93), which is now generally regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most offensive odour is given off from the ulcerated surface. The disease may be arrested spontaneously at any period of its progress, and long before so extensive a mutilation as that



Fig. 93.—Gangosa in a Cingalese. (*Orig.*)

described has been effected ; but it is always a long-standing and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared ; but although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age, but is rare in young adults, though Leyes states that in Guam he has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies—Dominica, for example (60 cases in a population of 2,000), Guam (1.5 per cent. of the population), the Carolines, Fiji, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

Goundou, or Anákhre ("Gros Nez").—In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhre. Later observations that have been made show that it has a wide distribution in Central Africa and South America, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Goundou usually commences during childhood, although adults also may be attacked. The earliest symptoms are



Fig. 94.—Case of goundou with periostitis of chin in negro girl; coexistent with tertiary yaws periostitis of tibiae. (Photo: C. C. Chesterman.)

severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils and the formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. Not so the paranasal swellings; these persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the eyes, may interfere with the line of vision and finally destroy these organs.

In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is not involved, being healthy-looking and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards. (Fig. 94.) The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected, resulting in the most hideous deformity. General glandular enlargement may be noted. Traumatism seems to predispose to the development of goundou.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but according to Botreau-Roussel and Clapier they are not entirely confined to this region: a similar hyperostosis may coexist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis arising from yaws, and recently spirochaetes have been demonstrated in sections of the bony growth, and it has been shown that goundou cases are immune to further inoculation with *T. pertenue*.

The general resemblance of goundou to leontiasis ossea has been remarked upon, and it must be distinguished from acromegaly and rickets.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer has operated with success upon 113 out of 130 cases observed on the French Ivory coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.



Fig. 95.—Distortion of fingers in tertiary yaws. (Orig.)

Periostitis, osteitis, and epiphysitis (Figs. 95, 96, 97).—Circumscribed painful periosteal nodes are frequently met with on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely tender, and the superjacent skin is tense and stretched. After the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may



Fig. 96.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws. (Orig.)

result in a sabre-shaped deformity of the long bones, especially the tibia, though occasionally the arms and fingers. A rarefying process is also at work, for such bones are subject to spontaneous fracture with resulting malunion. Such accidents are of common occurrence in those districts in which yaws is endemic. A chronic periostitis of the clavicle is of frequent occurrence in Fiji. These bone changes are accompanied by intense rheumatic

pains, and have received distinctive names, such as "sasala" (Fijian).

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are now regarded as a tertiary phenomenon of yaws (Spittel). Formerly they were regarded as constituting a disease *sui generis*. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 98). They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, and usually occur in the neighbourhood of the joints, but, according to Steiner, may occur scattered over the body. Similar lesions have been described in tertiary syphilis. In Africa they are apt to be mistaken for cysts of *Onchocerca volvulus*.

Skin lesions.—The healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited

to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as "melung." The contractions resulting from scar tissue may lead to partial ancylosis of joints, and in severe cases to the destruction of lymph-channels and the production of elephantiasis in the affected limb.

Synovitis.—A chronic synovitis, analogous to that of tertiary



Fig. 97.—Sabre-like deformity of tibia, radius, and ulna, and multiple cutaneous ulcerations, in yaws. (Orig.)

syphilis, often associated with bone lesions, and, it may be, with disorganization of the joint, may be noted.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not as a rule affected. Occasionally, however, there are debility and cachexia; or there may be enlargement and tenderness of the lymphatic glands. In other instances the rheumatic pains are a principal feature and may be very severe.

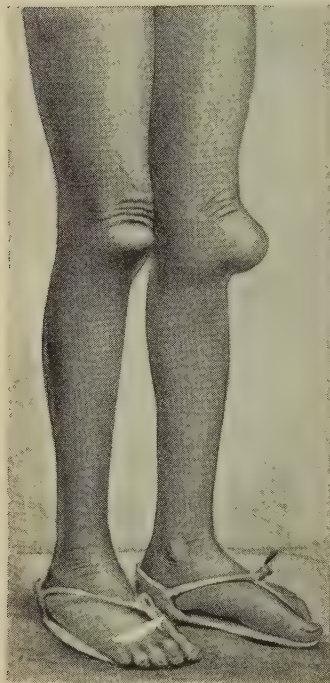


Fig. 98. — Juxta-articular nodules. (Photo: Dr. Watt.)

Immunity.—After the subsidence of the secondary stage a considerable degree of immunity is produced, but Sellards and Goodpasture have shown that this is relative only, for they successfully reinoculated patients with the disease who had undergone a course of salvarsan treatment. Apparently saturation of a community with yaws virus produces a relative immunity to syphilis. On these grounds may be explained the apparently well-authenticated fact that syphilis is absent amongst the Polynesians of Fiji, Tonga and Samoa, in whom yaws is especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them against subsequent attacks of the disease.

Duration and recurrences.—

Yaws lasts for weeks, or months, or years, its duration depending on the general health, idiosyncrasy, hygienic conditions, and the treatment employed. Mild cases in healthy subjects terminate in about six weeks; the average duration of an attack of yaws is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness and pains in the bones

and joints, and the successive crops may either be limited and partial in their distribution, or general.

Late manifestations.—Harper in Fiji believes that late manifestations of yaws occur as in syphilis, and that they produce neurological conditions resembling those of locomotor ataxia and general paralysis, but this view is not generally accepted.

Mortality.—Although in the literature of the subject reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be very small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted, red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point in connexion with yaws, as regards both diagnosis and etiology, is its relationship to *syphilis*. Both diseases may concur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws); and antecedent syphilis certainly does not confer immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases, as we have seen, gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be unknown. In yaws, Hutchinson's famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

The following table shows at a glance the main distinctions between this disease and syphilis (Spittel).

YAWS	SYPHILIS
Not congenital.	Congenital.
<i>Primary sore</i> —extragenital.	<i>Primary sore</i> —usually genital.
<i>Secondary stage</i>	<i>Secondary stage</i>
(a) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.	(a) Seldom imitates framboesia.
(b) Mucous membranes not affected.	(b) Mucous membranes affected.
(c) Itching common.	(c) Itching rare.
(d) Alopecia unknown.	(d) Alopecia may occur.
(e) Eyes unaffected.	(e) Iritis common; choroiditis and retinitis rare.

YAWS (*continued*)*Tertiary stage*

- (a) Visceral lesions absent.
- (b) Nervous system never seriously affected.
- (c) Blood-vessels: no endothelial proliferation as in syphilis.

Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.

Does not respond to mercury.

SYPHILIS (*continued*)*Tertiary stage*

- (a) Visceral lesions occur, i.e. pericellular cirrhosis, gumma of liver, kidney, etc.
- (b) Nervous system prone to infection: tabes, G.P.I.
- (c) Endarteritis obliterans of viscera—cerebral thrombosis.

Syphilis attacks constitution, affecting the vital structures.

Responds well to mercury.

Treatment.—All are agreed as to the propriety of endeavouring by good food, tonics, and occasional aperients to improve the general health. Most are agreed as to the propriety of endeavouring to procure a copious eruption by stimulating the functions of the skin by warm demulcent drinks; by a daily warm bath with plenty of soap; and, during the outcoming of the eruption, by such diaphoretics as liquor ammoniæ acetatis, guaiacum, etc. Warm clothing is indicated. In crab yaws a local application of 2-per-cent. tartar-emetic ointment in vaselin is very useful. Except where much bone destruction has taken place, salvarsan or, better still, its more recent and more soluble derivatives, have an almost magical curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is novarsenobillon. It is given intravenously to adults, and, if possible, to children; or intramuscularly (0.4 gm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are uncommon. It is curious to note that since the introduction of salvarsan the natives of the Congo are averse to receiving treatment till the secondary rash is well out. For adults the intravenous dose advocated is 0.9 gm., for young adults 0.6 gm., for children up to 10 years of age 0.3 gm., and for children under 2 years 0.1 gm. Some believe that the majority of cases do not require more than one injection. The systematic use of neosalvarsan in a yaws community would, if thoroughly carried out, promptly get rid of the endemic disease, and, wherever possible, should be enforced. The average time to effect a cure is given as eleven days. In Samoa it has been found necessary to give three injections of novarsenobillon of 0.6 gm. at weekly intervals for an adult male, and appropriately smaller doses for women and children. Babies are treated by intramuscular in-

jections. Moss in San Domingo has found that the cure after three injections is permanent. Apparently mercury and potassium iodide have little therapeutic action in yaws as compared with syphilis.

Stovarsol, which can be given by the mouth, is a much more convenient method of mass-treatment than injections of salvarsan. It is customary to commence with 1 grm. daily, increasing to $1\frac{1}{2}$, 2 and 3 grm. on successive days for adults; $\frac{1}{2}$ to 1 grm. for children. After a total amount of 8–15 grm., according to Van den Branden and Lefrou, the Wassermann reaction becomes negative. Chesterman considers three doses only are necessary to effect a cure, but finds that he can give in stovarsol ten times the corresponding dose of neosalvarsan. Slight diarrhoea is the only untoward symptom of intolerance occasionally observed, and he has given as much as 2 grm. to children at a single dose. One objection to stovarsol is that the full course may be more expensive than injections of salvarsan. *Holarsol* (May and Baker), oxy-amino-phenyl-dichlorarsine, in the form of subcutaneous injections in doses of 0.125 to 0.25 grm. for three doses at three- to four-day intervals has proved in Chesterman's hands to be extraordinarily efficacious in all stages of yaws.

Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate has led to the adoption of a similar method of treatment in yaws. The injection is given intramuscularly in an oily suspension containing 10 cg. of bismuth salt to the cubic centimetre; the preparation Trépol contains 64 per cent. of bismuth, while a more active one, known as Néo-Trépol, consists of precipitated bismuth in an isotonic glucose solution which diminishes local pain and liability to stomatitis. According to Shircore, Gilks, and Howard, two injections at weekly intervals are followed by favourable results in both secondary and tertiary yaws. The results appear almost to equal those obtainable with neosalvarsan. Injections should be made deep into the gluteus muscle, and occasionally some induration and abscess-formation may result. When treating natives on a large scale, a soluble form of sodium-bismuth tartrate,¹ which is now manufactured locally in East Africa, is preferable; 3 gr. dissolved in 3 c.c. of distilled water constitute a suitable dose for an adult; for children up to two years, $\frac{1}{2}$ –1 gr.; from two to eighteen years, 1–2 gr.; adults 2–3 gr.; and aged persons 1–2 gr. Children tolerate relatively larger doses than adults. In patients with septic mouths,

¹ This preparation, placed on the market by Howard & Sons, is known as "Sobita."

stomatitis and albuminuria are liable to ensue as a result of this treatment. This has been one of the greatest objections to the general use of bismuth, especially in the Solomon Islands and the Congo, combined with the fact that three or more injections are necessary. In the waging of a great anti-yaws campaign, as at present in Kenya and Tanganyika Territory, it has the undoubted advantage of cheapness, costing less than half-a-farthing a dose. According to Hanschell, stomatitis may be avoided if the injection is made into the deep subcutaneous tissues rather than intramuscularly.

Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are: the isolation and segregation of the affected; the dressing and treatment of wounds in the hitherto unaffected; the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of germs; the purifying or destruction by fire of houses or huts notoriously infected; the prevention of pollution of bathing-water by yaws discharges; and, especially, the prompt treatment by salvarsan, bismuth, etc., of the infected.

CHAPTER XXX

ULCERATING GRANULOMA OF THE PUDENDA

Synonyms.—Granuloma Venereum; Granuloma Inguinale.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and northern Australia; sporadically it occurs in the southern United States, on the West Coast of Africa, and in southern China.

Etiology.—There is good reason for believing that the disease is generally, though not invariably, a venereal one: very rarely have extragenital lesions been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragao in Brazil have described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures $1\ \mu$ by $0.2\ \mu$; it was described and named *Calymmatobacterium granulomatis* by Donovan, and later by Araujo. Later this organism was restudied by E. L. Walker, who found it to be a capsulated intracellular diplococcus, probably *Bacillus mucosus capsulatus*, one of the Friedländer group. It is easily cultivated on Sabouraud's medium after forty-eight hours' incubation, though it appears to thrive as well on other laboratory media. In the sores it is found in the deeper layers of the tissues. Cultures of the organism are pathogenic to mice and cause subcutaneous abscesses when injected into these animals; in rabbits they produce elevated nodules. There are reasons for believing that this organism represents merely a secondary infection, and that the main cause of ulcerating granuloma remains to be discovered.

Age and sex.—Ulcerating granuloma has not been recorded as occurring before puberty; it has been found only after the age of 13 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised.

Pathology.—Histologically this disease is allied to rhinoscleroma, and the close association between these two diseases in Sumatra has been emphasized by Snijders. On microscopical examination the new growth at the margins of the sore is found to be made up of nodules, or masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-

nests of Malpighian cells are embedded in a delicate fibrous reticulum. The nodular masses are, for the most part, covered by epithelium, their under-surfaces merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs of suppuration or of caseation, no giant cells, and no tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around the hair-follicles.

Symptoms.—The incubation period appears to be a comparatively short one, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere on the genitals, usually on the penis or labia minora, or on the groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin. The affected area, which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface prone to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous eccentric peripheral extension, and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces, particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 99). Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven, readily-breaking-down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally islands of active disease spring up in this scar tissue; but it is at the margin of the implicated patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin depigmented skin and thus show up as white patches.

In the case of the female (Fig. 100) the disease primarily attacks the crura of the clitoris, thence extending into the vagina, over the labia, and along the flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the

thighs. Occasionally the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum,

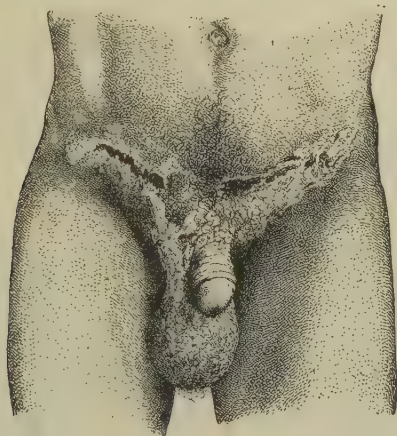


Fig. 99.—Ulcerating granuloma of pudenda in male.

and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times a profuse watery discharge exudes and even drips from the surface of the new growth, soiling

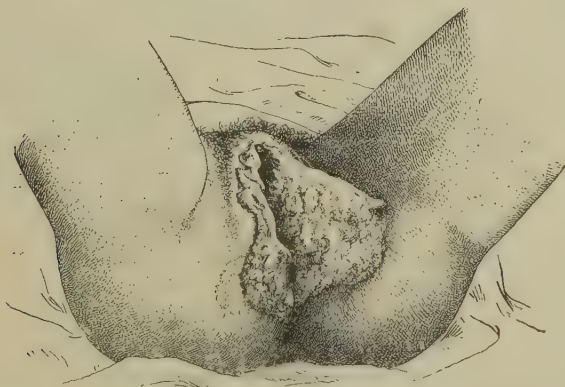


Fig. 100.—Ulcerating granuloma of pudenda in female.

the clothes, soddening the skin, and emitting a peculiarly offensive odour. In this condition the disease, slowly extending, continues

for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. (Fig. 101.) In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymph-channels may become blocked and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the urethra may result, and recto-vaginal fistulæ are common. It may cause death by eating its way into the bladder and causing septic pyelitis.

Diagnosis.—Malignant and syphilitic ulcerations of the groin



Fig. 101. Ulcerating granuloma : contact lesions on thigh showing characteristic features of the lesions. (*Orig.*)

are common enough; the disease under notice, however, differs widely from these—clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years; by absence of cachexia or of any tendency to cause death; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium. The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to the pudendal region; tends to follow in its extension the folds of the skin; is not associated with the tubercle bacillus, giant cells, caseation, or other evidences

of tuberculous disease. Unless complicated with a coincident syphilitic infection, which of course it may be, the Wassermann reaction is negative. The inefficiency of antisyphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed; but, although some improvement may be effected by these means, new nodules almost invariably spring up in the resulting cicatrix. Until recently complete excision, where practicable, offered the best chance of permanent cure; such a proceeding had to be undertaken before large areas and important passages had become involved.

Judging from its relatively superficial nature and close resemblance to lupus, it seemed probable that ulcerating granuloma might prove amenable to some form of radiotherapy. This is actually the case, and X-rays, originally suggested by Sequeira and Macleod, have been successfully employed in Madras, though in some cases they appear to exert no effect whatsoever. Treatment by intravenous injections of tartar emetic, introduced by Aragao and Vianna in 1913, has also proved remarkably successful; improvement usually sets in, and, although in a small proportion of cases relapse occurs, in the vast majority the cure is radical. The drug should be given as in kala-azar (*see* p. 147), but the amount requisite to effect a cure varies within wide limits. The Editor has had one case with a limited suprapubic lesion which healed completely after a total of $17\frac{1}{2}$ gr. of antimony tartrate had been given altogether, while other cases require 170 gr. or more. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Apparently stibacetin and other pentavalent compounds of antimony ("von Heyden 471") are more efficacious than tartar emetic. From 3 to 4 grm. of the drug are necessary in order to promote a cure. The Editor has found it advisable to dress the open granulations daily with an ointment containing 1 per cent.¹ of antimony tartrate in white vaselin. It should be left on the sore for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Intermittent dressing with eusol helps to keep the surface clean. Radiant heat applied to the ulceration has proved beneficial, while touching indolent spots

¹ To make antimony-tartrate ointment, the necessary amount of antimony tartrate is first dissolved in a small quantity of liquid paraffin and then made up to strength with white vaselin. The ointment must not be spread on the healthy skin.

with a silver-nitrate stick will sometimes promote healing. When the sore is of limited extent, excision and subsequent skin-grafting may be advisable, but a wide margin of healthy skin should be removed, or recurrence will most certainly take place. Tartar emetic treatment may be combined with X-rays and with "protein-shock" treatment (Hanschell). Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary. When the growth invades the perineal space in the female, the actual cautery may be the only means of limiting extension of the process.

Prophylaxis.—As this disease is most certainly spread by sexual connexion, prevention consists in the avoidance of illicit intercourse, especially with native women.

Section V.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XXXI

PARASITES OF THE CIRCULATORY SYSTEM: SCHISTO- SOMIASIS

Definition.—A group of diseases caused by certain digenetic trematodes of the family Schistosomidæ which inhabit the venous system of man in various tropical and subtropical countries.

I. SCHISTOSOMIASIS OF THE BLADDER DUE TO *SCHISTOSOMA* *HÆMATOBIMUM*

Synonyms.—Bilharziasis ; Bilharziosis ; Bilharzia Disease ; Endemic Hæmaturia.

Definition.—A chronic endemic disease produced by infection of the pelvic veins, particularly those of the bladder, and occasionally those of the rectum, by *Schistosoma hæmatobium*, the eggs of which, being deposited in the mucous membrane of the bladder, give rise to hæmaturia and cystitis or other symptoms connected with the urinary organs, and occasionally, when deposited in the rectum, to muco-sanguineous discharges from the bowel. The eggs of the parasite are discharged in the urine and, in certain cases, in the fæces.

History.—Hæmaturia has been known to exist in Egypt since the earliest times, and the eggs of this parasite have been found in mummies by Rüffer. Bilharz, in 1851, originally discovered the parasite, which was named *Bilharzia* by Cobbold, but this designation was found to be invalid, as the genus *Schistosoma* of Weinland already had priority.

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Sudan, Uganda, the Congo, and Rhodesia ; it is met with in West Africa as well.

In North Africa it is especially common in Morocco, Algiers, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, Persia, Mesopotamia, Cyprus, in the town of Tavira in Portugal, in Mauritius, Réunion, and Madagascar. A few indigenous cases have been reported from Western Australia. In Egypt it is present in quite one-half of the population. (Map V.)

Etiology. *Parasite.*—*Schistosoma hæmatobium* is a unisexual trematode. The male measures 1–1·5 cm. in length by 1 mm. in breadth; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. (Fig. 102.) The female, darker in colour, but 2–2·5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. The parasites live in the blood of the portal vein and its mesenteric branches, but numbers dwell also in the pubic, vesical, and uterine plexuses. (Fig. 103.)

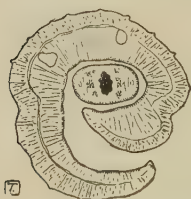


Fig. 102. — *Schistosoma hæmatobium*. Diagram of transverse section of male and included female.

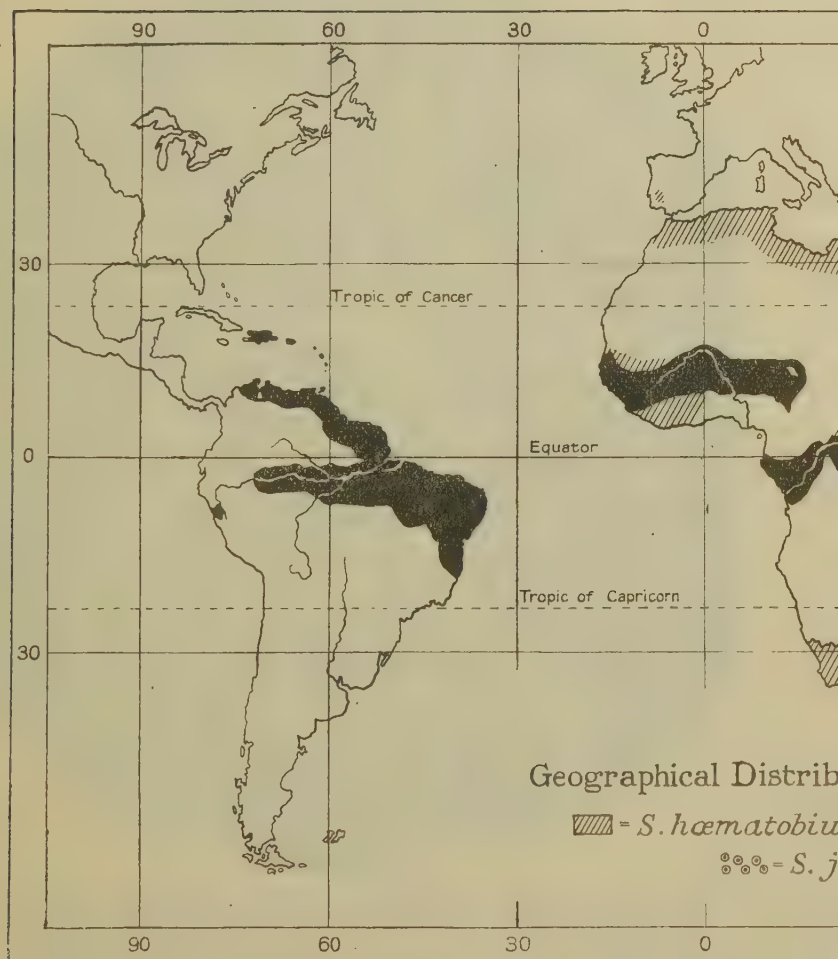
The eggs are oval, and are provided at one end with a definite spine. They measure 0·16 mm. in length by 0·06 mm. in breadth. Normally they are voided in the urine, exceptionally in the fæces.

Life-history.—On coming into contact with water, the eggs hatch and give rise to an active, ciliated embryo or miracidium,

which, as a rule, enters a fresh-water snail belonging, usually, to the genus *Bullinus*; in the liver and hermaphrodite gland of this mollusc it develops into sporocysts, and eventually into active, bifid-tailed cercariæ which, on escaping from the snail, re-enter man by burrowing through the skin. (For further details regarding the life-history of this parasite, see p. 723.)

It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure of the fluid; a 0·75-per-cent. salt solution completely inhibits the process.

Pathology.—The character of the changes brought about by the schistosome varies very much according to the degree and the duration of the infection. In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs even in the minute blood-vessels. Later, especially in the trigone of the bladder, there are present rounded patches of inflammatory thickening which project somewhat, are granular on the



surface, and dense in consistence; on section they creak under the knife as if they contain gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which the microscope reveals scattered throughout their entire extent.



Fig. 103. — Microscopic section of bladder-wall showing (*Schistosoma haematobium*, males and females, *in situ*, in a large vein, (Micro-photo: Dr. H. B. Newham.)

The eggs are principally deposited in the submucosa, less extensively in the mucous membrane itself, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a sort of connective-tissue capsule; or they may be lying in small blood-vessels which they occlude. Some eggs are seen

to have undergone calcification; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches already mentioned, phosphatic deposits, also containing eggs, are not uncommon; sometimes the patches present minute sloughs. (Fig. 104.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villousities and different forms



Fig. 104. Section of bladder-wall, showing eggs of *S. hæmatobium* in tissues.

of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded in lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly towards their lower ends, even at an early stage of this disease. In rare instances the pelvis of the kidney itself is affected. Obliteration of the ureter, both from small stones and from thickening of the mucous membrane, has sometimes been met with; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

Hyperplasia from schistosome infestation may also occur in the vesiculæ seminales, in the walls of the vagina, and in the cervix of the uterus, leading to corresponding bloody, egg-containing discharges.

Schistosome eggs in small numbers have been found in the liver, in gall-stones, in the heart, and in the kidneys. The occasional occurrence of eggs in the brain, spinal cord, and lungs has already been noted. Tumours of schistosome origin have sometimes been met with in connection with the peritoneum and ligaments of the uterus.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3-per-cent. potash solution.

Symptoms.—The symptoms produced by *S. hæmatobium* vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever; in other instances the suffering is very great. Indirectly, from the serious nature of the lesions of the urinary organs to which it may give rise, this schistosome is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. The *incubation period* of definite organic disease, on the other hand, varies within wide limits from three months up to two-and-a-half years.

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes, however, the hæmorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic spined eggs.

In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining; these invariably contain eggs. A low power of the microscope suffices, and is best for diagnosis.

Pain is by no means always a predominant feature; when

it occurs it generally assumes the form of a dull sense of oppression in the suprapubic region, deep-seated perineal pain, or scalding on micturition. Frequency of micturition is an early, and urgency a very common symptom. Rectal symptoms, with passage of blood and mucus, may coexist with the urinary symptoms, and a digital examination may detect ulceration above the prostatic lobes. This localized lesion may be due to *S. hæmatobium* alone, though it must be remembered that mixed infections of *S. hæmatobium* and *S. mansoni* are very common, especially in the Nile Valley. Sometimes adult worms *in copula* are passed in the urine; this generally occurs after a copious hæmorrhage due to a ruptured vessel.

Endemic hæmaturia lasts for months or years. Spontaneous recovery is rarely complete. In ordinary cases, provided no re-infection takes place, the hæmaturia tends to decrease, although eggs may continue for years to be found in the last few drops of urine passed. In severe cases, sooner or later, signs of cystitis supervene and give rise to a great deal of suffering. Not infrequently the eggs become the nuclei for stone, and symptoms of urinary calculus are superadded. (Fig. 105.) Sometimes the pathological changes induced by the presence of the parasite in the

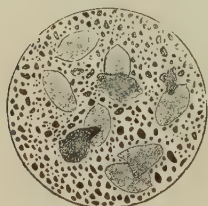


Fig. 105.—Section through nucleus of urinary calculus containing eggs of *Schistosoma hæmatobium*.

bladder lead to the development of new growth, in which event the symptoms become more urgent and the hæmaturia perhaps excessive. Hypertrophy, contraction, and even dilatation of the bladder are not unusual. Besides the bladder symptoms there may be signs of prostatic disease, or of disease of the vesiculæ seminales causing spermatorrhœa. In the latter case, eggs may be detected in the semen. In other instances the ureters and kidneys become involved, resulting in ureteric dilatation and hydronephrosis

(Plate XXVIII). Secondary septic infection of the urinary tract with septic cystitis commonly supervenes. From the suffering attending these aggravated forms of infection, the patients become anæmic, wasted, debilitated, and a ready prey to intercurrent disease.

Milton has pointed out the extreme frequency of urinary fistula in Egypt, the result of schistosome disease of the urethra. These fistulæ may occur anywhere in the neighbourhood of the genitals, but are especially common in the perineum and posterior surface of the scrotum, and originate from infiltration



URINARY SCHISTOSOMIASIS.

Radiographic appearances of ureteric and vesical calculi. Note outline of bladder; *u*, ureteric orifice; 1, infiltrated folds of ureter; 2, calculi in ureter and in bladder; 3, papillomata and calculi.

Key to PLATE XXVIII



URINARY SCHISTOSOMIASIS.

(By permission of Dr. G. O. Lotsy.)

PLATE XXVIII

(See Key, facing.)

by eggs of the pubic tissue or roof of the urethra just in front of the bulb, the eggs of the parasite being deposited in the mucous or submucous tissue. Stricture of the urethra is by no means uncommon from a similar cause, especially in the case of fistulæ connected with the floor of the urethra. In the male, infiltration of the penile sheath may result in an elephantoid condition with chordee and actual obstruction to the urinary flow. (Fig. 106.)

Ferguson has pointed out the liability of bilharzial tumours to develop malignant changes.

Vaginitis and cervicitis have been produced by this parasite. Papillary growths and ulcers may be mistaken for carcinoma. On the vulva, papillomatous masses containing schistosome eggs are, according to Madden, common. Similar excrescences about the anus and in the groin and perineum, require microscopical examination to be distinguished from venereal warts.

Large numbers of eggs, as pointed out by Turner, may be deposited in the lungs, where they give rise to a form of interstitial pneumonia. They have been found also in the brain and spinal cord, thus accounting for epileptic and paralytic symptoms from which the patients had suffered during life; such symptoms supervene only in hyperinfected individuals.

Chesterman has recorded districts in the Congo where the eggs of *S. hæmatobium* are found in the fæces only, and give rise to dysenteric symptoms closely resembling those produced by *S. mansoni*. The eggs themselves in this instance, singularly enough, are longer and with more attenuated extremities than are those usually found in the urine. There is no evidence at present that the parasite is specifically distinct, and the intermediary host appears to be *Bullinus africanus*. Harvey Pirie has described deposition of eggs in the appendix, where they have given rise to symptoms of acute appendicitis.

Diagnosis.—The diagnosis of this disease is not difficult; the presence of eggs in the urine is decisive. In countries like Egypt, where the disease must often concur with chyluria, with stone, with vesical tumour, with gonorrhoeal cystitis, and with pyelitis, as well as with prostatic disease, care must be exercised in each



Fig. 106.—Urinary schistosomiasis: pseudo-elephantiasis of penis, due to infiltration by ova. (After Madden.)

particular case to separate the special factors to which the various symptoms are attributable. Thus, in chyluria concurring with schistosome disease there will be chyle in the urine in addition to blood. In such a combination the clot which forms will be larger, will contain oil granules and globules, and very probably microfilariæ, in addition to schistosome eggs; moreover, the microfilariæ will generally be detectable in the finger blood if looked for at night. Stone in the bladder, when suspected, has to be searched for with the sound. In gonorrhœal cystitis the history of gonorrhœa will be forthcoming. In prostatic disease enlargement of the prostate may be made out. Difficulty may sometimes arise when eggs are few in number, or when they have ceased altogether to come away in consequence of the death of the parent worms. The mischief wrought by the parasite remains, although the eggs—the most certain evidence of the parasite's previous presence—may be discharged no longer. But, even if eggs are very few, they may still be found in the last drop or two of urine passed. If they are no longer to be found in the urine, sometimes, by scratching the surface of the bladder with a sound and examining the shreds of mucus so obtained, a few, calcified it may be, but presenting the characteristic spine, may be seen with the microscope.

Fairley's reaction.—Fairley in 1917 described a complement-deviation reaction by employing as antigen an extract of the livers of infected snails (*Planorbis boissyi*). The antigen is prepared by macerating a number of livers containing cercariæ of *S. mansoni* in absolute alcohol, filtering, and evaporating by means of a Sprengel's pump. A saline extract is then made of the dried residue and the anti-complementary dose estimated. The general technique employed is the same as for the quantitative Wassermann reaction in syphilis.

The reaction is apparently a group reaction, in so far that an antigen prepared from cercariæ of *S. mansoni* will give positive results with *S. hæmatobium* serum in 89 per cent. of early cases; further, Bettencourt and Borges have recently stated that a similar reaction takes place with an antigen made from *Fasciola hepatica*. A positive result may be obtained in early infections before the appearance of eggs in the dejecta. It is not so specific in the later as in the earlier stages of the disease, and may be utilized, as Fairley has shown, as an efficient check to treatment.

Intradermal reaction.—Recently Fairley has described a new intradermal test, similar to the Casoni reaction in hydatid. A saline extract of dried livers, 0.5-per-cent., of *Planorbis exustus* infected with *S. spindalis* is used. The extract having been rendered bacteria-free by passage through a filter,

is injected intradermally in a dose of 4 min. A positive reaction is characterized by an immediate wheal and a zone of erythema, and in from five to eighteen hours there appears a delayed type of reaction. The test is useful as a means of diagnosis in all forms of schistosomiasis and apparently persists for years after the patient has been cured.

Cystoscopic examination.—In the early stages of the localized disease (within two months of infection) the cystoscope reveals sparse grey discrete elevations in the trigone around the ureteric orifices; later, definite hæmorrhagic papules appear with surrounding inflammation. Later still, characteristic "sandy patches" resembling ridges of sea-sand and papillomata can be distinguished.

Prognosis.—An important element to be considered in venturing on a prognosis is the long life of the parasite. Another important element in prognosis is the degree of infection: the greater the number of parasites, the more severe and the more extensive is the disease they produce. As with filarial infection, the greater the number of cases in a district, the greater the proportionate probability of severe infections being met with. The prognosis is practically that of a chronic cystitis depending on a remediable, and not in itself fatal cause. Much suffering may often be produced, and, as a consequence, anæmia and debility. Possibly calculus may be formed; possibly grave renal disease may ensue; possibly villous or epitheliomatous growths in the bladder. In the milder degrees of infection, which fortunately are the commonest, the patient seems to be in no way inconvenienced by the parasite, and generally escapes all serious consequences. In any case, mild or severe, there may be attacks of hæmaturia from time to time; as a rule, the quantity of blood lost is insignificant.

Treatment.—The successful treatment of schistosomiasis, by the intravenous injection of sodium-antimony tartrate, is due to Christopherson. His results have been abundantly confirmed. The drug appears to act upon the adult trematode by cumulative action, and the results of treatment are judged by observation upon the eggs in the urine. From observations made by Dye, the adult stage of the parasite is most readily affected by tartar emetic; cercariæ and miracidia are less susceptible, while the eggs are not affected to anything like the same degree.¹ For this purpose the freshly-passed urinary deposit is mingled daily with about sixty times as much warm water at 130° F., and the hatching of the eggs is observed. Under normal conditions hatching takes place in about five minutes, but after injections of antimony

¹ Christopherson does not agree with this statement, believing that the changes in the eggs are produced by the direct action of antimony, quite apart from any effect of the change upon the generative organs of the female schistosome.

tartrate it is found that such eggs as appear in the urine are dark and shrivelled and contain dead miracidia. Christopherson, as already noted, believes this change to be due to the direct action of antimony upon the eggs. (Fig. 107.) Fairley, from experimental slides on the allied *S. spindalis* of the goat, believes that antimony acts in a selective manner upon the reproductive organs of the female schistosome, and thus causes firstly, the shrunken appearance of the egg, and secondly, cessation of egg-laying capacity.

It should be noted that living eggs left in too long contact with alkaline urine fail to hatch; therefore all experiments should be performed with freshly-voided urine.



Fig. 107.—Egg of *Schistosoma hæmatobium*, showing changes produced in contained miracidium by antimony tartrate. (Dr. John Anderson.)

The intravenous injections are given on alternate days over a period of four to six weeks. It is usual to begin with $\frac{1}{2}$ gr. of tartar emetic dissolved in 10 c.c. of freshly-distilled and sterile water, and gradually to increase the amount by $\frac{1}{2}$ gr. at a time till a maximum individual dose of 2–2 $\frac{1}{2}$ gr. is reached. It is not necessary always to dilute to 10 c.c.; for amounts under 1 gr., 6 c.c. of distilled water are quite sufficient. Care should be taken not to boil antimony tartrate for any length of time or subject it to steam pressure. In injecting large numbers of natives the stock solution of tartar emetic is made up in a sterilized vaccine bottle with a rubber cap in a strength of $\frac{1}{2}$ gr. to 1 c.c. of distilled water; for use this is diluted with 5 c.c. of

water. The solution should be drawn into a syringe of 10 c.c. capacity, and slowly injected into the median basilic or cephalic vein (see p. 664). The total amount injected to kill all the trematodes should be 25–30 gr. of tartar emetic. A rapid improvement in the condition of the urine is soon observed; generally all traces of blood disappear after the injection of 15 gr. For children a total of 10 gr. appears to be sufficient; the maximum individual dose being 1 gr. The course, once commenced, should be persisted in; cases almost invariably relapse if interruptions occur, lasting a week or more. In Egypt (1925) the course consists of twelve injections given three times weekly till 22 $\frac{1}{2}$ gr. of the drug have been administered; it occupies four weeks. When a small amount of diluent fluid is utilized, as suggested, only slight evidences of

toxic absorption are noted, such as headache, cough, nausea and transient rheumatic pains, especially in shoulder joints.

Fairley has amply confirmed the specific action of tartar emetic on adult schistosomes. In *S. spindalis* infections of the goat, he has shown that tartar emetic in doses of 3·9 to 5·5 mg. per kilo at daily intervals for a period of from sixteen to twenty-six days is capable of killing off the adult schistosomes and eradicating the disease.

Emetine hydrochloride.—There is evidence that emetine also is toxic to the schistosome (Diamantis and Erian). The injections should be given intramuscularly to children who are intolerant of antimony, or whose veins are too narrow for intravenous injections; generally one commences with $\frac{1}{2}$ -gr. doses, the maximum single dose for a child being 1 gr., while an aggregate total of 15–20 gr. may be given. Tsykalas, who has reported results in 2,000 cases, injects the drug intravenously in doses of $1\frac{1}{2}$ gr. daily, the total course lasting 8–10 days, and 15–17 gr. being given. Toxic symptoms—diarrhoea, vomiting and neuritis—are apt to ensue.

Fairley states that as a result of experimental studies on an allied species, *S. spindalis* of the goat, emetine given intravenously, ten to fifteen injections varying between 0·7 and 1 mg. per kilo of body-weight, causes the rapid death of the parasites, and is much more efficacious than tartar emetic.

In Sierra Leone, Gordon has recorded excellent results in children infected with *S. hæmotobium* with subcutaneous injections of emetine hydrochloride, $\frac{1}{2}$ gr. daily for fifteen days, and that moreover powder emetine periodide, 2 gr., thrice daily for fifteen days, appeared to be equally efficacious. In view of mass treatment of the diseases in natives, where intravenous therapy is impracticable, the latter observation is of great importance.

Local applications are useful. Stone and troublesome new growths are to be removed by operation. When distress is extreme, Mackie and others have had good results from perineal cystotomy and drainage. Perineal fistula must be dealt with on ordinary surgical principles. Hyperplasia in the vagina and cervix is best treated by scraping. Provided reinfection be avoided by the exercise of prudence in the matter of water, there is no necessity for sending the patient with this disease away from the country in which the parasite was acquired.

Prophylaxis.—In the endemic districts, children, in particular, should be carefully and repeatedly warned against drinking or bathing in rivers, ponds, and canals. (Fig. 108.) Sportsmen should be warned against wading, especially when engaged in shooting snipe, in localities known to be infected; even fishing in fresh-water canals in countries like Egypt is not free from risk. Swamps, when slightly brackish, are safe. Drinking-water should be boiled, and every care must be exercised to prevent the diffusion of the disease by prohibiting the evacuation of excreta into or near water where the miracidia might find the opportunity of development and

transmission. This prohibition should not be restricted to patients exhibiting definite symptoms of the disease, but extended to all, because, as special inquiries have shown, a large proportion of



Fig 108.—The intermediary hosts of *S. hæmatobium* and *S. mansoni* (*Planorbis boissyi* and *Bullinus contortus*) in their natural surroundings. Nat size. (J. K. Lund, del.)

the infected do not suffer from any troublesome symptom and are often unaware of their infection. Leiper points out that much might be accomplished by attacking the mollusc intermediary and the free cercaria. As regards the former, he suggests periodic drying

of irrigation canals and the use of chemical manures; and as regards the latter, the use of cercariacides such as sulphate-of-soda tablets for drinking-water, and boiling, and lysol, creolin, or cresol (1 : 10,000) for bathing-water. Chlorine, in the strength (1 : 1,000,000) generally used in tropical countries to sterilize water, appears to have no effect upon the living cercaria; the addition of larger quantities renders it unpotable. The free cercaria lives but a short time—at most forty-eight hours—in water, but a mollusc once infected continues so for months. The free cercariæ readily pass through the ordinary municipal filter-bed, for they can traverse 30 in. of fine sand in five hours; but they perish, as has been stated, if they do not get access to an appropriate host within forty-eight hours. These facts should be taken into account by the sanitarian.

Fairley has recently pointed out that both tartar emetic and emetine hydrochloride exert a lethal effect upon bilharzia cercariæ, which is greatly enhanced in the presence of human serum. Possibly these drugs may exert a prophylactic as well as a therapeutic effect.

II. INTESTINAL SCHISTOSOMIASIS DUE TO *SCHISTOSOMA MANSONI*.

Definition.—A chronic endemic disease caused by *Schistosoma mansoni*, giving rise to dysenteric and other symptoms referable to the intestinal canal, and characterized by the eggs of the parasite in the fæces. In the early stages there may be general symptoms, such as fever and urticaria, indicating absorption of the toxins excreted by the adult parasites.

History and geographical distribution.—The occurrence of a schistosome producing lateral-spined eggs was noticed by Bilharz in 1851, but he founded it with *S. hæmatobium*; subsequently several observers encountered female worms with lateral-spined eggs in utero, and the idea of a distinct species suggested itself to Sonsino and others; but this idea was at once discarded for other hypotheses—for instance, that the peculiar position of the spine was due to distortion of the egg-shell in passing through the muscular coat of the rectum.

Manson, in 1903, found numerous lateral-spined eggs in the fæces of a patient from Antigua who had never suffered from hæmaturia. The peculiarities of the case led him to think that the lateral-spined egg indicated a new species of schistosome. In 1907 Sambon, on comparing specimens of the type characterized by lateral-spined egg with *S. hæmatobium* and other schistosomes, and taking into consideration its peculiar geographical distribution and distinct pathogeny, proposed that it should be considered a distinct species—*Schistosoma mansoni*. He subsequently described many cases of lateral-spined schistosomiasis from South America. Holcomb and da Silva first described the peculiar anatomical distinctions of *S. mansoni*, but the duality of species was finally settled by Leiper in 1916. He proved

that the miracidia, hatching from lateral-spined eggs, after developing in snails of the genus *Planorbis*, developed into adults with constant morphological distinctions. Since then this work has been confirmed by Fairley and the Editor in Egypt, and by Lutz in Brazil.

Possibly this schistosome is originally a West African species, imported into the New World by African negroes. Its geographical distribution, as far as is known at the present day, extends from the Nile Valley throughout Central and West Africa, the West Indies, and South America; most probably its range of distribution is limited by that of an appropriate intermediary host of the genus *Planorbis*. (Map V.)

Etiology.—The parasite much resembles *S. hæmatobium*. The distinguishing features are that it is generally smaller in size and more grossly tuberculated. There are minor distinguishing features. (Fig. 109.) The female deposits one or two eggs at a time—a circumstance perhaps explicable by the peculiar structure of the uterus. The eggs are somewhat spindle-shaped, are provided with a lateral spine (Plate XXXV, 12, facing p. 874) and are generally slightly shorter than those of *S. hæmatobium*, 0.15 mm. in length by 0.06 mm. in diameter. These eggs are passed out in the fæces, rarely in the urine, and hatch out a ciliated miracidium.

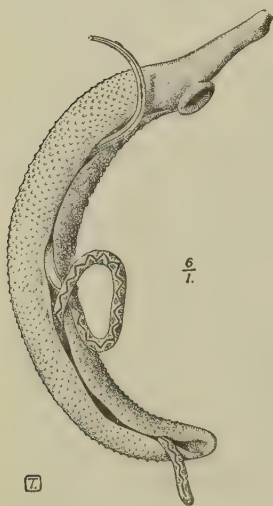


Fig. 109. — *Schistosoma mansoni*, male and female. (Partly after Looss.)

Pathology.—The eggs of *S. mansoni* may be found in great numbers in the liver, where they give rise to a peculiar form of “pipe-stem” cirrhosis. Sandy patches, due to effete calcified eggs, cover large areas of the intestinal surface, and may give rise to acute choleraic diarrhoea. Deposits of black pigment granules take place in the interstitial and secreting cells of the liver, and have been

shown by Fairley to occur in both *S. mansoni* and *S. hæmatobium* infections, but to be commoner and more abundant in the former. The lymph-glands in the latter situation and in the retroperitoneal tissue are enlarged. There is generally an appreciable hypertrophy of the spleen, which may possibly be attributable to toxic absorption.

The affections of the colon may be classified into four types—(a) those with simple thickening of the mucous membrane; (b) thickening of the mucosa with papilloma-formation; (c) pericolic

tumours associated with papillomata; (d) polypi of the cæcum which may lead to intussusception.

Symptoms.—*S. mansoni* inhabits chiefly the branches of the portal vein in the liver, and the mesenteric veins. Its eggs, deposited within the submucous layer of the rectum, give rise to dysenteric-like symptoms, commencing six to eight weeks after infection (Fairley); mucus with blood is passed from time to time, the egg-laden stools becoming frequent and their passage perhaps being attended with tenesmus. In certain well-established cases small (sometimes large) branching, soft growths are to be felt inside the sphincter ani. They resemble polypoid growths and are apt to be mistaken for piles. They may extend as high up the bowel as the sigmoid flexure. On tearing up one of these growths one can see the eggs in the debris. (Fig. 110.)

In mass infections, in early cases, toxic symptoms resembling those of katayama disease (p. 530) are noted, especially in Europeans. The general symptoms consist of a remittent pyrexia, with urticaria, marked abdominal pain, anorexia, rigors, and pulmonary symptoms. A pronounced leucocytosis with a high eosinophilia (up to 76 per cent.) has been reported. (Chart 29, p. 317.)

Later, localized symptoms with passage of dysenteric motions supervene.

In the terminal stages of the disease large abdominal tumours may form, easily palpable, and actual intestinal stasis or distension may take place. Infiltration of the buttocks with eggs, leading to induration and fistulæ, is not uncommon. When the liver has become markedly cirrhotic, ascites may be present. Pneumonia from egg deposition in the lungs is an occasional complication.

Sometimes the dysenteric attacks may develop into acute diarrhoea of a choleraic type, which may prove fatal.

Hepatic cirrhosis and splenomegaly.—Dye has described in a certain limited area in northern Nyasaland a form of hepatic cirrhosis with splenomegaly, terminating in many instances fatally, and especially affecting children. The eggs of the schistosome are



Fig. 110.—Rectal schistosomiasis: adenomata prolapsed through anus. (After Madden.)

found in great numbers in the liver, but not in the spleen. Apparently this stage of the disease is similar to the fully developed schistosomiasis japonica (see p. 532).

Diagnosis.—The characteristic eggs are easily found in the fæces under a low power of the microscope; they may be very scanty, and it is necessary to examine three or more specimens before arriving at a negative diagnosis. (Fig. 111.) They are more easily found in solid than in fluid motions, especially in the outer portions of a scybalum. Quite a high proportion of cases are latent—that is to say, they do not present any of the more urgent symptoms.



Fig. 111.—Microphoto of miracidium of *Schistosoma mansoni* escaping from egg. $\times 1,500$. (Dr. A. J. Chalmers.)

Fülleborn recommends the Telemann method of finding the eggs when scanty in the fæces: the fæces are shaken up with a mixture of concentrated hydrochloric acid 1 part, water 1 part, ether 2 parts, and strained through gauze; the filtrate is centrifuged and examined.

In about 5 per cent. of cases in Egypt the characteristic eggs may be found in the urine as well as in the fæces.

The complement-deviation reaction is the same as in *S. hæmatobium* infections (p. 518).

In rectal disease, should *S. mansoni* be suspected, one of the

adenomatous growths may be removed by means of forceps and examined for eggs.

Sigmoidoscopic examination may reveal a pedunculated adenopapillomatous growth in the upper part of the rectum, but usually this is unnecessary, as the growth can be felt by digital examination alone and may be seen protruding in polypoid masses from the anus. The localized thickening of the large intestine, due to polypi and pericolic growths, can be palpated in heavily infected subjects through the abdominal wall. They are more generally situated in the transverse and pelvic colon than elsewhere.

Treatment.—Gross changes in the organs are more extensive than in *S. hæmatobium* infections, due partly to toxic absorption and partly to deposition of eggs, and it is possible, as Madden and Day have reported from Egypt, for the adult worms to be killed by tartar-emetic treatment but for the effects of their presence to remain. Hence it may prove necessary to operate upon polypoid or adenomatous growths obstructing the intestinal lumen. In early cases antimony is as successful as it is in cases of *S. hæmatobium*. Lampe in Surinam treats out-patients with three injections of 3 c.c., 5 c.c. and 7.5 c.c. of a one-per-cent. solution of tartar emetic thrice weekly, with a total of 150–200 c.c., the whole course occupying six to seven weeks. Dye and others have tried rectal injections of tartar emetic as being especially applicable to small children, who can take 16 gr. by the rectum without toxic effects, but the amount of the drug absorbed by this method is unknown. Five to seven daily injections are necessary.

Emetine.—Apparently emetine is as efficacious in this disease as it is in *S. hæmatobium* infections. The amount necessary, according to Maciel, is about 0.6 grm. (9.2 gr.) in a series of ten injections. The initial two injections should be $\frac{1}{2}$ gr. each, the remainder 1 gr. Emetine should be reserved for use in those cases who are intolerant of tartar emetic.

Dolbey and Fahmy hold that the only rational method of obtaining a permanent cure in cases with extensive disease of the rectum is to excise the whole tube of mucous membrane. Lengths of 12–15 in. can be removed with ease. A circular incision is made at the junction of skin and anal mucous membrane; the external sphincter and levator ani attachment are separated by blunt dissection: when once the latter has been separated, the mucous tube may be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Recovery is uneventful; there is little tendency to retraction of the tube, and control of the

anal sphincter is regained. This operation is unsuitable for very anæmic or debilitated patients.

Prognosis.—This is the same as for *S. hæmatobium*, but it must be remembered that the disease generally assumes a latent form, and that even large intestinal polypi may give rise to little or no inconvenience.

Cases with papillomata of the rectum, dysenteric symptoms, tenesmus, and anæmia, and those with actual obstruction of the intestinal canal and cirrhotic changes in the liver, must be regarded as serious.

Prophylaxis is the same as in *S. hæmatobium* (p. 521). There appears to be a greater probability of contracting the disease in the neighbourhood of muddy canals that are the favourite haunt of planorbis, of which a high proportion (50 per cent. or more in some cases) are found to be infected with the cercariæ of this trematode in Egypt.

III. VISCERAL SCHISTOSOMIASIS DUE TO *SCHISTOSOMA MANSONI*

Synonym.—Egyptian Splenomegaly.

Definition.—A common disease in Egypt and Northern Nyasaland, possessing many features resembling infantile kala-azar; causing anæmia, febrile disturbances, cirrhosis of the liver, and ascites, and probably due to infection with *Schistosoma mansoni*.

Geographical distribution and etiology.—Splenomegaly associated with cirrhosis of the liver is common in all parts of Upper and Lower Egypt, where 20 per cent. of infants under 4 years of age are found to have splenic enlargement and anæmia. It is common at all ages among the working class up to 30; in the young it is apt to run a severe course, while at a later age the chronic form, progressing to ascites, is met with. In children the disease is generally associated with rickets: in adults, with ancylostomiasis. A somewhat similar disease has been recorded by Dye from Northern Nyasaland in patients infected with *Schistosoma mansoni*. Day also came to the conclusion that in Egypt this disease is a peculiar manifestation of *S. mansoni* infection. He regards it as distinct from Banti's disease in that the hepatic changes are noted from the commencement, while the eosinophilia and recurrent fever disappear under specific treatment with tartar emetic. The hyperplasia of the spleen appears to be secondary to the hepatic cirrhosis, and to the pathological condition of this organ are to be ascribed the anæmia and leucopenia which are found in advanced cases of the disease. The patients with advanced

cirrhosis are just those who have few intestinal symptoms, and who pass scanty, or it may be, no eggs in the stools. Eggs of *S. mansoni* may be found on digestion of solid organs, such as the liver and spleen, with potash.

Symptoms.—The symptoms appear to be more objective than subjective. There are irregular fever, wasting, and a striking pallor. The spleen is obviously enlarged, hard, and firm, often reaching to the umbilicus (Fig. 112); the liver also in the early stages is enlarged. Vomiting and diarrhoea are frequent. In the later stages oedemas of varying degree and purpuric rashes may ensue. The fever is generally irregular in type, intermittent, and not amenable to quinine. The splenic enlargement causes pain and discomfort, especially after meals, and on exertion gives rise to a dragging sensation, though the symptoms are caused by debility and anæmia. As the disease progresses, so the pyrexia increases, till the steady enlargement of the liver and spleen causes the costal angle to expand. Hæmatemesis often occurs, but jaundice is rare. The final stage is ushered in by cirrhotic changes in the liver, which becomes hard and firm, and shrinks within the costal margin. The spleen also becomes fibrotic, but does not proportionately decrease in size. The pain, which is due to perisplenitis and perihepatic adhesions, increases, while vomiting is a common feature. Finally, the patient succumbs with all the symptoms of an hepatic cirrhosis, ascites, and emaciation. Death is usually due to pulmonary complications.

The blood picture varies at different stages of the disease. In the early stages there is a distinct leucocytosis of 17,000, and myelocytes may be present; later a progressive anæmia of the chlorotic type becomes apparent with a leucopenia of 3,000 and a mononuclear increase of 10–17 per cent.



Fig. 112. — Egyptian splenomegaly.
(After Richards and Day; by permission of "Brit. Journ. Surg.")

Among the rare complications, thrombosis of the portal vein and hepatic carcinoma have been recorded.

The course of the disease is generally protracted: in older children and adults it may run twenty years or more. Ascites is always regarded as an unfavourable symptom.

Morbid anatomy and pathology.—Ferguson says that the average weight of the spleen is 30 oz.; it may reach 300 oz., and, according to Day, may contain a few eggs of *S. mansoni*. It is firm in consistency; microscopically there is a general hyperplasia with active phagocytosis of the red cells by macrophages. The liver is usually enlarged in the early stages, and presents the picture of early multilobular cirrhosis with isolated necrotic foci. In the more advanced stages the organ is shrunken and firmly fixed to the diaphragm by adhesions. There is a comparative absence of bile-duct formation. The bone-marrow shows no great disturbance of the hæmatopoietic system.

Diagnosis.—This must be made upon clinical grounds. Usually it is not difficult to demonstrate the characteristic eggs in the tissues. Visceral syphilis must be borne in mind.

Treatment—According to Richards, in cases with ascites, palliative operative interference, such as frequent tapping and the Talma-Morrison operation (omentopexy), is permissible. In early cases, before the development of ascites, Owen Richards originally performed splenectomy with success. Coleman, Bateman and Stiven have since confirmed the value of this operation. The mortality rate is about 15 per cent. and deaths are due to late shock. Great care is still necessary in the selection and preparation of cases for operation. Ascites, pellagra, heart disease and debility are contraindications. A considerable leucocytosis should be considered a bar to operation, and it is necessary to differentiate the condition from leukæmia. An injection of pneumococcal vaccine should be given the night before the operation to prevent the development of this complication. The weight of the spleens removed by these surgeons averaged $3\frac{3}{4}$ lb. The favourable effects appear to be permanent, and ascites does not develop. Day claims that early cases are curable with tartar emetic. His observations on the etiology of the disease still await further confirmation. The disease naturally tends to become arrested after some years duration.

IV. EASTERN SCHISTOSOMIASIS DUE TO *SCHISTOSOMA JAPONICUM*.

Synonym.—Katayama Disease.

Definition.—A chronic endemic disease of Eastern Asiatic countries, caused by *Schistosoma japonicum*, and characterized by great enlargement of the liver and spleen and the development

of ascites. The eggs of the parasite are discharged in the fæces. Initial toxic symptoms, urticaria and pyrexia, are commonly observed.

History and geographical distribution.—For very many years an endemic disease characterized by splenomegaly, enlargement of the liver, cachexia, ascites, pyrexia, and dysenteric symptoms had been observed. In 1888 Majima found eggs in a cirrhotic liver, and in 1904 Katsurada saw a miracidium emerge from similar eggs which he had found in fæces; later he discovered the adult trematode, *S. japonicum*, in the portal veins of the cat. In that year Catto noted similar parasites at the autopsy of a Chinaman in Singapore. The next addition to our knowledge was made by Katsurada, who succeeded in communicating the parasite to cats by immersing their legs in the water of certain ponds reputed to convey the disease. In 1913 Miyairi and Suzuki traced the parasite, through a snail common in the infected districts, back to the vertebrate host; an observation confirmed in the following year by Leiper and Atkinson.

So far, the parasite has been found principally in Chinese and Japanese, though a few Europeans—mostly naval officers and sportsmen, addicted to snipe-shooting in the rice-fields—have acquired the disease. Its present range, as far as is known, may be stated as follows: In China it occurs in endemic foci in the Yangtse basin, from Ichang, 350 miles above Hankow, to the sea; in the provinces of Hunan (Siang River), Hupeh, Anhwei, Kiangsu, and Kiangsi. An endemic centre has recently been reported from Shiuchow, on the North River near Canton. It has been recorded on the Burmese border between Yunnan and the northern Shan States. In Japan it is especially prevalent in the province of Hiroshima and in the village of Katayama. Endemic foci also exist in southern Formosa, and in the southern Philippine Islands—Samar, Leyte, and Mindanao. (Map V.) In countries where it exists, dogs, cats, rats, and imported cattle are found naturally infected; native cows, on the other hand, appear to be immune.

Etiology.—The parasite closely resembles *S. hæmatobium*, though it is smaller and the integument is smooth and non-tuberculated. In proportion, the acetabulum or ventral sucker is longer than in either *S. hæmatobium* or *S. mansoni*. The eggs, smooth and slightly oval, measure 0·08 mm. by 0·06 mm., and pass through the intestines into the fæces. They possess a rudimentary lateral spine, and show considerable variation in size, but in the uterus of the female schistosome they are much smaller.

The miracidium, after casting its cilia, develops in fresh-water molluscs of the genus *Oncomelania*,¹ Gredler, 1881, which has a widespread distribution in Japan and China; probably all species of this genus are potential carriers of *S. japonicum*.

Pathology.—The outstanding feature is the great enlargement of the liver and spleen. The former is hypertrophied and nodular, from the formation and contraction of fibrous tissue; on digesting

¹ There has been much confusion as to the correct nomenclature of these snails; the reader is referred to Appendix, p. 733.

with 3-per-cent. potash solution it is found to contain many eggs. The great enlargement of the spleen, on the other hand, is probably due to absorption of toxins or, possibly, to back-pressure, as eggs are seldom found in this organ. Granules of black pigment are found in both viscera. The appendices epiploicæ are greatly thickened and may be matted together; the mesenteric and retroperitoneal

lymph-glands are enlarged; hypertrophy and thickening of the lower parts of the intestinal tract, with formation of ulcers and polypoid growths filled with eggs, are generally noted. The bladder is unaffected.

Occasionally, indurations of the pia mater and lesions of the cerebral cortex have been found. The young forms of the parasite enter the general circulation through the veins and collect in the lungs, and apparently enter the liver by traversing the mediastinum and the diaphragm. Inside the portal system they soon reach maturity. (Plate XXIX.) Infection of the foetus during intra-uterine life is apparently possible.

Symptoms.—The disease produced by *S. japonicum* is a serious one and, when pronounced, sooner or later proves fatal. The gravity of any given case will depend, amongst other things, on the degree of infection and the circumstances of the patient. Of 1,077 persons near Shushima, Japan, examined by Koiki, 42 were found infected. Of these 42, only 22 were not in good health. Penetration of the skin by the cercariæ causes an



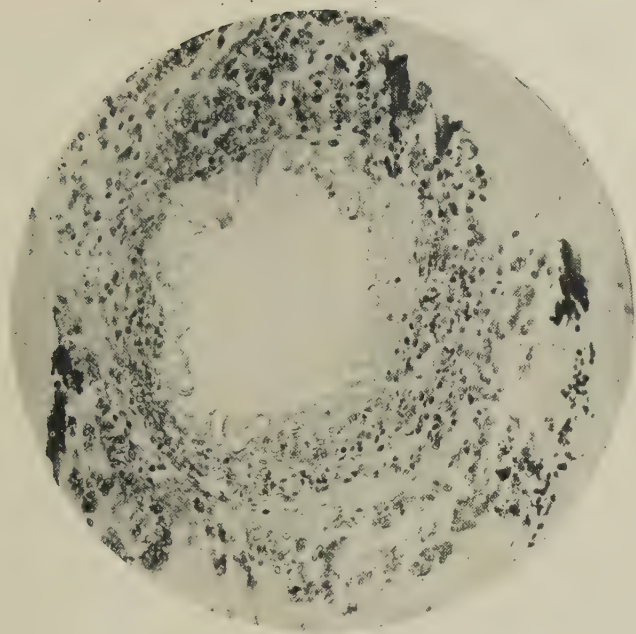
Fig. 113. — Asiatic schistosomiasis (Photo: Dr. J. A. Thomson; courtesy of Wellcome Bur. Sci. Res.)

intense pruritus, partly mechanical, and partly due to an irritating substance secreted by the larvæ. The erythema thus produced was formerly regarded by the Japanese as a skin disease, "kabure." The same happens after infection with the cercariæ of the other two human schistosomes—*S. mansoni* and *S. hæmatobium*.

The course of the disease can be divided into three stages. The *first* occurs within a short period of infection and lasts about



Schistosoma japonicum in vessels of mesentery.
(Microphoto: Dr. Henderson.)



Eggs of *Schistosoma japonicum* embedded in walls of appendix vermiformis. (Microphoto: Dr. Kerr.)

SCHISTOSOMIASIS OF THE FAR EAST.

a month. It is associated with toxic symptoms such as pyrexia, urticaria, abdominal pain, paroxysmal cough, a leucocytosis, and a high eosinophilia (60 per cent. or more). Dermatographia is common. The *second* stage is characterized by great emaciation and is accompanied by dysenteric symptoms and enlargement of the liver and spleen. The *third* or final stage, when it does supervene, occurs from three to five years after infection. In this the liver and spleen are cirrhotic and enlarged. Ascites and œdema of the extremities appear, with anæmia and exacerbations of the dysenteric symptoms. (Fig. 113.) The patient may die of exhaustion or of some terminal infection. Jacksonian fits, due to deposition of eggs in the brain cortex, and hemiplegia have been described.

Diagnosis.—All cases of urticarial fever from the endemic districts should be watched for many months (especially if eosinophilia

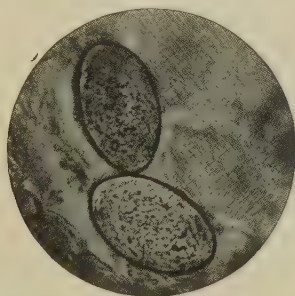


Fig. 114 —Eggs of *S. japonicum* in faeces. $\times 250$. (Photo: Dr. J. Bell.)

persists after the subsidence of the primary attack) and the stools examined for eggs of *S. japonicum*. All cases of chronic intestinal disturbance, especially if associated with enlargement of liver and spleen, from the districts mentioned should be regarded as, possibly, cases of schistosomiasis, and the blood and stools should be examined. If the characteristic eggs (Fig. 114) are discovered the diagnosis is established.

A complement-deviation reaction, as in *S. hæmatobium*, with antigen made from cercariæ, may be employed; and a similar reaction results with extracts from the bodies of the adult trematodes when the serum of an artificially-infected horse is employed (Suezasu, 1917). According to Faust and Meleney, the "formaldehyde or aldehyde test" is strongly positive in many cases.

It is said that ferments are given off by the body of the trematode, one of which is allied to trypsin, and digests albumin in an alkaline medium.

Treatment.—Antimony tartrate, given in the same doses and in the same manner as for *S. hæmatobium*, appears to be equally efficacious in killing off the adult trematodes. A total amount of 24 gr. or more is necessary. In a case under the care of the Editor, Jacksonian fits disappeared after treatment. According to Faust and Meleney, 22–30 gr. of intravenous tartar-emetic over a period of eighteen to twenty days is usually curative.

Unfortunately, in China and Japan cases only apply for treatment when in the advanced stages of the disease; in these the intestinal ulceration and the hepatic cirrhosis are generally so pronounced that this treatment is of little avail.

Emetine.—Probably injections of *emetine hydroch oride* are as efficacious as in the other schistosome infections; but it is necessary to remember that, as Failey has shown experimentally in goats, fatal verminous thrombosis of the pancreatic and portal veins, as the result of the presence of dead parasites, may occur.

Tootell has reported favourable results from intravenous injection of “mercurochrome 220 soluble”—on a basis of $2\frac{1}{2}$ c.c. of a 1-per-cent. solution for every eleven pounds of body-weight.

Prophylaxis.—Water reported to cause the disease should be boiled, or avoided, for drinking or bathing purposes. Sportsmen, if they must wade in such waters, should wear long boots or water-proof waders. According to Narabayashi, lime in a solution of 1:1,000 is the most economical reagent available for the extermination of the intermediary host, and kills the cercariæ in thirty minutes. It is especially recommended because of its value as a fertilizer. It is said that the eggs remain viable for ten days outside the body in a solid motion, and this factor should be recognized in formulating sanitary measures. Specific treatment in out-patient clinics will help to eliminate carriers of the disease, whilst educational propaganda, especially in China, is all-important.



1, *Mf. bancrofti* ; 2, *mf. perstans* ; 3, *mf. loa* ;
4, *mf. ozzardi*.

MICROFILARIÆ OF THE BLOOD.

PLATE XXX

CHAPTER XXXII

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES: FILARIASIS

Definition.—Morbid conditions produced by certain nematode worms, or filariæ, the adults of which, of both sexes, live in the lymphatics, connective tissues, or mesentery, producing live embryos or microfilariæ, which find their way into the bloodstream, where they are capable of living for a considerable time without developing further.

History.—In 1863 Demarquay found what is now known as the embryonic form—microfilaria bancrofti (Plate XXX, Fig. 1) in hydrocele fluid, and in 1866 Wücherer discovered the same organism in chylous urine. In 1872 Lewis established the fact that the organism lives principally in the blood of man, and consequently named it *Filaria sanguinis hominis*. The adult was found in 1876 by Bancroft in Brisbane, and named *Filaria bancrofti* by Cobbold.

Manson in 1878 made the important observation that the mosquito subserved the parasite as intermediary host, and in 1880 described the remarkable phenomenon of filarial periodicity.

Originally Manson proposed to call the embryonic form of *Filaria bancrofti*, in order to emphasize its nocturnal periodicity, *Filaria nocturna*, but, in accordance with the rules governing zoological nomenclature, precedence must be given to Cobbold's name for the adult form; the embryonic form is therefore referred to in this manual as microfilaria bancrofti; the other filariæ of the blood are named microfilaria loa (or mf. diurna) (Plate XXX, Fig. 3), microfilaria ozzardi (mf. demarquayi) (Plate XXX, Fig. 4), and microfilaria perstans, the embryo of *Acanthocheilonema perstans* (Plate XXX, Fig. 2, and Map VI).

Pathological importance.—Only one of these parasites, so far as we know at present, appears to have important pathological bearings, viz. *F. bancrofti*, which, in its adult stage, inhabits the lymphatics of man. There is abundant reason to believe that *F. bancrofti* is the cause of endemic chyluria, of various forms of lymphatic varix, and of other obscure tropical diseases, including tropical elephantiasis.

The filariæ less important from a pathological standpoint are dealt with in the Appendix (pp. 779, 786).

I. FILARIASIS DUE TO *FILARIA BANCROFTI*

Geographical distribution and prevalence.—*F. bancrofti* occurs indigenously in almost every tropical and subtropical country, from Charleston in the United States and southern Spain in Europe to Brisbane in Australia. It is extremely common in India and South China, Samoa, and many of the Pacific islands, where fully 60 per cent. of the inhabitants are affected.

If the individuals who exhibit the microfilaria in their blood be reckoned in addition to those who exhibit the pathological effects of filarial disease, but in whose blood the microfilaria is no longer to be found, the incidence of filarial disease in some of the Pacific islands is a very high one—as high as 80 per cent. The parasite is common in South America, the West Indies, West and Central Africa. (Map VI.)

Etiology. Parental forms.—The parent filariæ (*F. bancrofti*) have been found many times. They are long, hair-like, transparent



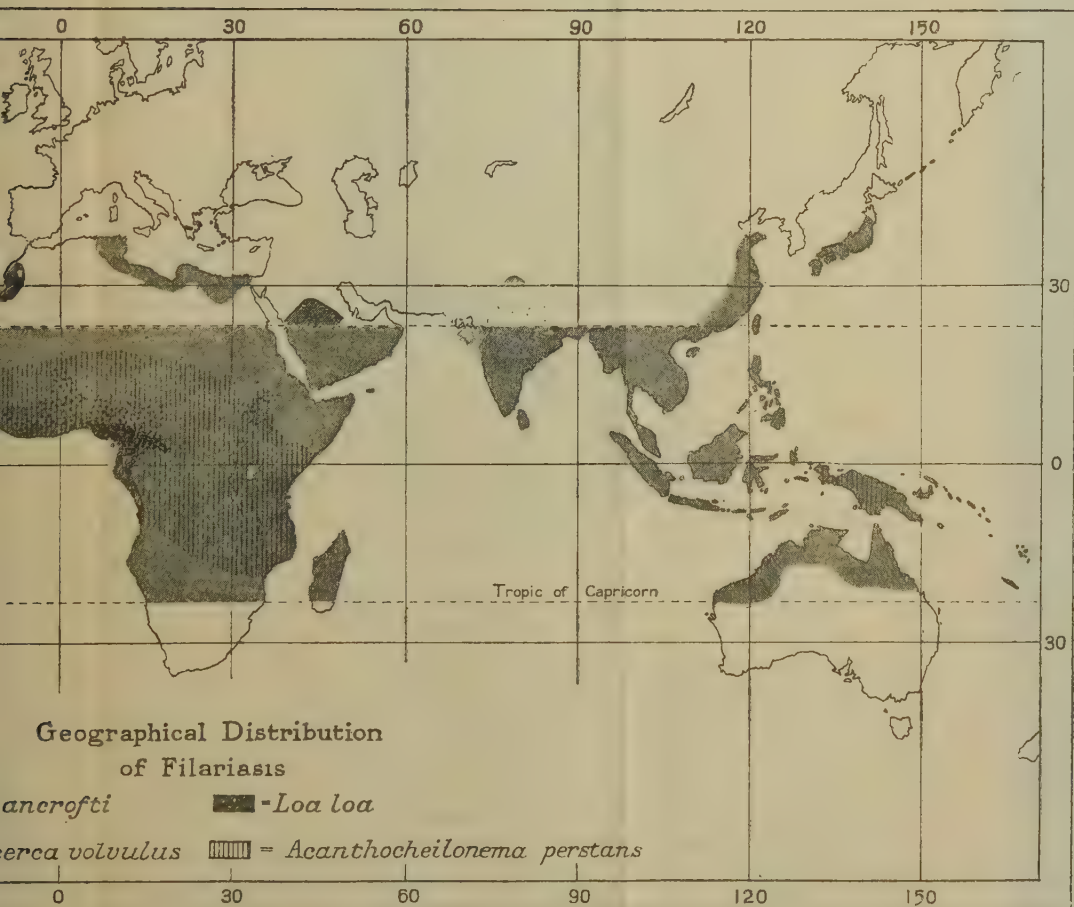
Fig. 115.—*F. bancrofti* (natural size): *a*, male; *b*, female.

nematodes, 3–4 in. in length (Fig. 115). The sexes live together, often inextricably coiled about each other. Sometimes they are enclosed, coiled up several in a bunch and tightly packed, in little cyst-like dilatations of the distal lymphatics (Maitland); sometimes they lie more loosely in lymphatic varices; sometimes they inhabit the larger lymphatic trunks between the glands, the lymphatic glands themselves, and, probably not infrequently, the thoracic duct.

The female worm is almost twice the length of the male, and considerably broader. The fully-mature and fecundated female filaria gives birth during her lifetime to an unending stream of living embryos or microfilariae, which emerge from the vaginal orifice coiled up in their chorionic envelopes. (For further details, see Appendix, p. 773.)

The life-spans of *F. bancrofti* and its microfilariae have not been determined. From the fact that the microfilariae have been found in the blood many years after the opportunity of infection has passed, it is to be concluded that both of them may live for many years. The embryo filariæ sometimes disappear completely from the circulation within a few hours of the death of the parent





MAP VI

Cribb & Co.

worms during an attack of lymphangitis. Nothing is known of what becomes of the microfilariæ when they grow effete or die.

As shown by Wise and the Editor, the mature worm is cretified after its death, and may be found in this condition in the lymphatic vessels and glands, sometimes in large numbers. (Fig. 116.)

The microfilariæ.—When present in large numbers in the blood-stream, microfilariæ may be recognized in wet film preparations; but, when the parasites are scanty, for the examination of a large number of persons it is



Fig. 116. — Calcified *Filaria bancrofti* lying in and blocking a lymphatic vessel. (Orig.)

often necessary to examine a considerable quantity of blood (20 c.mm.) in thick-drop preparations, dried and then de hæmoglobinized. When seen in fresh blood the embryo filaria is a snake-like organism which, without materially changing its position, wriggles about very actively.

When dead and stained, the embryo is seen to be enclosed in a sheath (Fig. 117). On measurement, it is found to be a little under 0.3 mm. in length, in breadth about the diameter of a red blood-corpuscle. At the anterior extremity of the living microfilaria can be seen a minute spicule, which is shot out and as rapidly retracted, and it is thought by some that the head is sheathed by a serrated "prepuce." In a fresh blood preparation the spicule can be seen disturbing cells at some distance away. (Figs. 118, 119.)

Filarial periodicity.—A singular feature in the life of the microfilariasis what is known as “filarial periodicity.”

If, under normal conditions of health and habit, the blood be

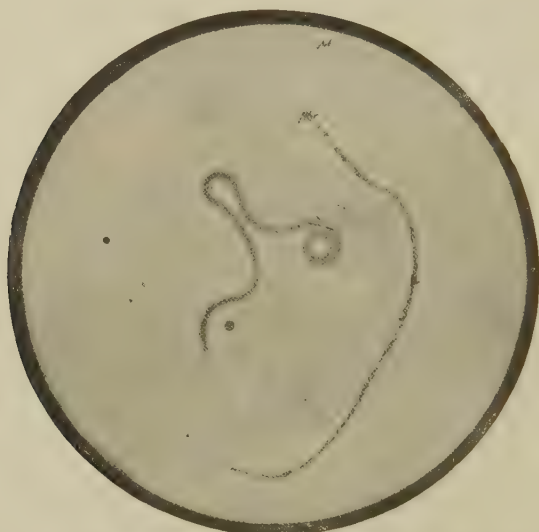


Fig. 117.—*Microfilaria bancrofti* in hydrocele fluid. The embryo on the right has escaped from its sheath. (*Orig.*)

examined during the day, the microfilaria is rarely seen, or, if it be seen, only one or two specimens at most are encountered in a slide.



Fig. 118. —Structure of head end of *microfilaria perstans* (*a, b*) and of *microfilaria bancrofti* (*c, d*).

But towards evening they begin to appear in gradually increasing numbers. The swarm goes on increasing until about midnight, at which time it is no unusual thing to find as many as three hundred,

or even six hundred in every drop of blood ; so that it has been calculated that as many as forty or fifty millions are simultaneously circulating in the blood-vessels. After midnight the numbers begin gradually to decrease ; by eight or nine o'clock in the morning the microfilariae have disappeared from the peripheral blood for the day. This nocturnal periodicity, under normal conditions, is maintained with the utmost regularity for years. Should, however, as Mackenzie has shown, a filarial subject be made to sleep during the day and remain awake at night, the periodicity is reversed ; that is to say, the parasites come into the blood during the day

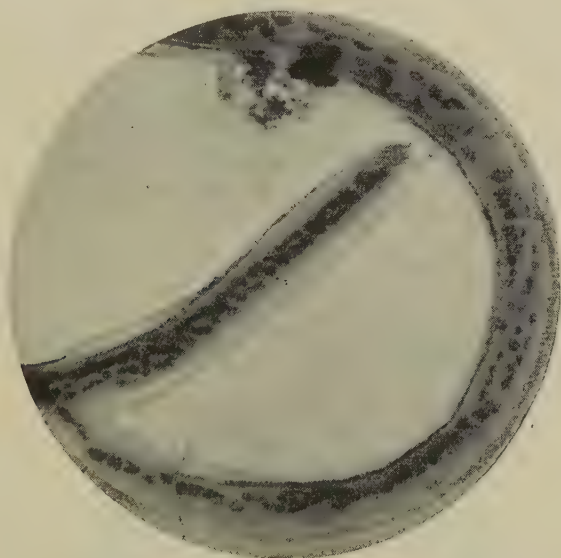


Fig. 119.—*Microfilaria bancrofti*, showing spicule. $\times 1,000$.

and disappear from it during the night. It cannot be the sleeping state, as some have conjectured, that brings about this periodicity ; for the ingress of the microfilariae into the peripheral blood commences three or four hours before the usual time for sleep, and the egress several hours before sleep is concluded, and this egress is not complete until several hours after the usual time of waking. This night swarming of the embryos of *F. bancrofti* in the peripheral circulation is apparently an adaptation correlated to the life-habits of its liberating agent, the mosquito *Culex fatigans*, its usual intermediary host. (Chart 33.)

Many years ago Manson had an opportunity of ascertaining

that during their diurnal temporary absence from the peripheral circulation the microfilariae retire principally to the larger arteries

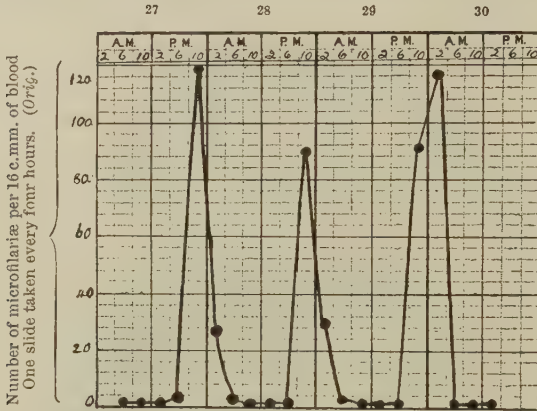


Chart 33.—Filariasis (*F. bancrofti*, *microfilaria nocturna*), showing nocturnal periodicity.

and to the lungs, where, during the day, they may be found in enormous numbers.

In lung sections (Fig. 120) the microfilariae lie outstretched or variously coiled in the vessels, large and small. In the heart-muscle they are found in



Fig. 120—Section of lung showing microfilariae in blood-vessels. (Microphoto: Dr. Spitta.)

the capillaries between the fibres; in the kidneys they seem especially to affect the Malpighian tufts; a very few are also found in the capillaries of the brain; vast numbers are present in smears from the inner surface of the carotid arteries. Preparations afford no explanation as to how the microfilariæ contrive to maintain their position in the blood-current, or as to the forces determining their peculiar distribution.

Subsequent observations have shown that, though microfilariæ can be demonstrated in the capillaries of the liver and spleen in small numbers, the capillaries of the lung and kidney (Anderson) appear to be the favourite habitat of the embryos of *F. bancrofti*, and of other species which do not exhibit this extraordinary nocturnal periodicity. Thus, the non-periodic Pacific microfilaria (see below) has also been found in greatest abundance in these situations.

Various theories have been advanced by Fülleborn and others to account for this singular phenomenon, though none are entirely satisfactory. Yorke and Blacklock think that obstruction to the passage of microfilariæ through the cutaneous vessels is at a minimum at the end of the period of bodily activity, and that the periodicity is primarily dependent upon the variations in the actual supply of microfilariæ to the cutaneous vessels. But how account for the diurnal periodicity of microfilaria loa in circumstances which are exactly the reverse, or for the non-periodicity of the Pacific form of *F. bancrofti*?

Non-periodic microfilaria bancrofti.—Formerly it was thought that nocturnal periodicity was uniformly observed by the microfilaria of *F. bancrofti* at all times and in every country. Many years ago Thorpe remarked that in Tonga and Fiji the microfilaria could be found often in great abundance in the blood during the daytime, but, strange to say, it has been ascertained that the filariæ of neighbouring islands in the Pacific—namely, the Solomons, some parts of New Guinea and of the Bismarck Archipelago—are for the most part, though not entirely, periodic.

The Editor demonstrated that the microfilariæ of Indian immigrants who have acquired their filarial infections in India retain their periodic habits during at least three years of residence in Fiji, but that if an Indian or a Solomon Islander acquires the infection in Fiji the microfilariæ are non-periodic in habit.

As an explanation of this striking anomaly, it has been suggested that the non-periodic microfilaria is the progeny of a parent worm specifically distinct from *F. bancrofti*; but Leiper failed to find any anatomical difference between the Fijian worm and the *F. bancrofti* of India, China, and South America. Fülleborn and the Editor, after minute study and comparison of the histology of the microfilariæ from those countries, find that they are identical in every respect. It may be, as the Editor suggested, that the non-periodic habit of the Pacific microfilaria is a partial adaptation to the day-habit of the usual intermediary of the parasite in Fiji and other

Pacific islands — *Aedes variegatus* (*Stegomyia pseudoscutellaris*) (Plate XXXI). These observations have been abundantly confirmed by O'Connor, who has established the significant fact that the range of the non-periodic filaria is coextensive with that of its intermediary host, *Aedes variegatus*, in the Pacific.

The mosquito the intermediary host of F. bancrofti.—Should the females of certain species of mosquito¹ (*Culex fatigans*² or *Aedes variegatus*) which have fed on the blood of a filaria-infected person be examined immediately after feeding, the blood con-



Fig. 121.—Microfilariae casting their sheaths.

tained in the stomach will be found to harbour large numbers of living microfilariae, while a few hours afterwards it will be seen that many of them are actively engaged in endeavouring to escape from their sheaths. The change in the viscosity of the blood seems to prompt them to endeavour to effect their escape. After a time the majority succeed in effecting a breach and in wriggling themselves free from the sheaths which had hitherto enclosed them (Fig. 121). This process can be induced by chilling wet blood preparations on ice and then allowing them to thaw at room-temperature. The microfilariae now, having become free, move about from place to place. At a somewhat later period it will be observed that, after discarding their sheaths, they have quitted the stomach and entered the thoracic

muscles of the mosquito, where they may be seen moving languidly. To detect this, one should dissect the insects in normal saline solution, for if distilled water is used, the larval worms break up by osmosis. In the thorax of the insect the parasite enters on a metamorphosis which takes from ten to twenty days (according to atmospheric temperature) to complete, eventuating in the formation of a mouth, of an alimentary canal, and of a peculiar trilobed caudal end, as well as in

¹ For a complete list of species which may serve as intermediary hosts, see Appendix, p. 776.

² In China, *Culex pipiens* (see p. 814).



AÈDES (STEGOMYIA) VARIEGATUS.

The buckled-up proboscis sheath is shown as in act of biting.

PLATE XXXI



a relatively enormous increase in size (to $\frac{1}{16}$ in.) and activity. The larval filariæ now leave the thorax, and the majority pass forwards by the prothorax and neck, and, entering the head, coil themselves up close to the base of the proboscis beneath the pharynx and cephalic ganglia, though a few find their way into the abdomen, and even into the legs. Low first showed that the filaria, in its future progress, enters the proboscis, where, as pointed out by Grassi, its exact position is the interior of the proboscis-sheath (labium). (Fig. 122.)

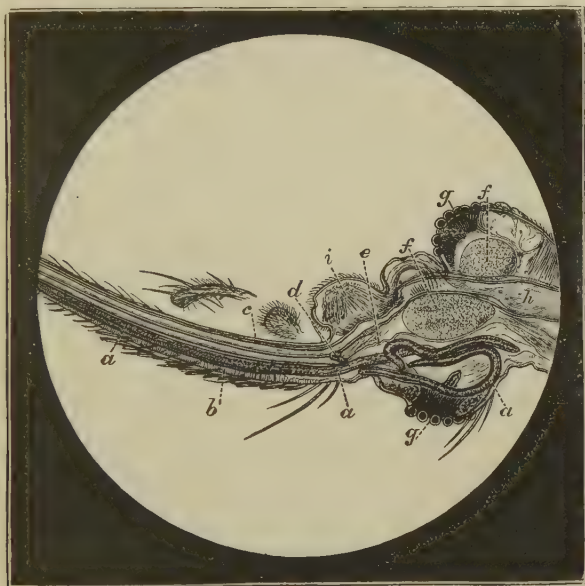


Fig. 122.—*F. bancrofti* in head and proboscis of mosquito. (G. C. Low.)

a, a, *a*, Filariæ; *b*, labium; *c*, labrum; *d*, base of hypopharynx; *e*, duct of veneno-salivary gland; *f, f*, cephalic ganglia; *g, g*, eye; *h*, oesophagus; *i*, pharyngeal muscle.

The parasites remain in this position, awaiting an opportunity to enter a warm-blooded vertebrate host, when the mosquito next proceeds to feed. This they appear to do by penetrating the thin membrane that unites the labella to the tip of the proboscis-sheath, and so pass on to the surface of the skin, which they penetrate in the neighbourhood of the puncture made by the mosquito. As pointed out by Annett and Dutton, there is a weak point in the chitinous skeleton of the labium just where the labella are joined on, and it is at this weak spot that the parasites escape. Sometimes the larval filaria, in its progress through the thorax, becomes arrested

and dies; the defunct worm then appears to become enclosed, like a mummy, in a case of chitin inside the mosquito's body, resulting in the curious structure represented in Fig. 123.

These observations prove that, like the malaria parasite, the filaria is introduced into its human host through the agency of a mosquito-bite. Once introduced into the human body, the filaria finds its way into the lymphatics and glands. Arrived in one of these, it attains sexual maturity; possibly, though no exact data

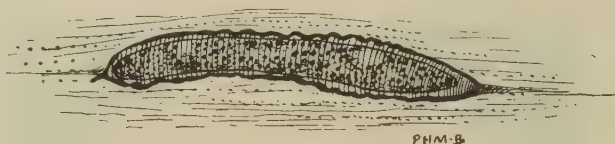


Fig. 123.—Chitinized filaria in thorax of mosquito.

are available, after a period of six months or more fecundation is effected, and in due course new generations of larval filariæ are poured into the lymph. These, passing through the gland—if such should intervene—by way of the thoracic duct and left subclavian vein, or by the lymphatics of the upper part of the body, finally enter the circulation.

Epidemiology and endemiology.—In most countries in which filariasis is common it appears to be the rule that the incidence of infection is greatest in the male sex, though, in British Guiana, Daniels and Conyers reported twice as many females infected as males. This exception to the general rule probably finds an explanation in the habits of the natives. The Editor's statistics from Fiji show that of 1,320 people of Fijian blood, 30·4 per cent. of males and 23·9 per cent. of females were filariated. The incidence is greatest in both sexes after the twentieth year; comparatively more females than males are infected below the age of 10. The youngest infected subject is one recorded by Anderson and his colleagues—a child of 14 months. The rate of filariation varies considerably in different islands of the Pacific, and even in different districts of the same island, and is in direct proportion to the incidence of elephantiasis and other filarial diseases. In an investigation conducted in 1912 in Ceylon the Editor found that, whereas 26 per cent. of the adults of some of the villages were infected, in neighbouring ones the inhabitants were quite free from the parasite and its associated diseases.

Pathology. *The filaria not generally pathogenic.*—In most cases of filarial infection the parasite exercises no manifest injurious influ-

ence whatever. In a certain proportion of instances, however, there can be no doubt that it does have a very prejudicial effect on its host, and this mainly by obstructing lymphatics. The healthy, fully-formed microfilariæ—that is to say, the embryonic filariæ which, by means of the microscope, we see in the blood—have, so far as we can tell, no pathogenic properties whatever.

Filarial disease originating in injury of lymphatic systems.—Roughly speaking, the filaria causes two types of disease: one characterized by varicosity of lymphatics, the other by more or less solid oedema. The exact way in which the parasite operates has

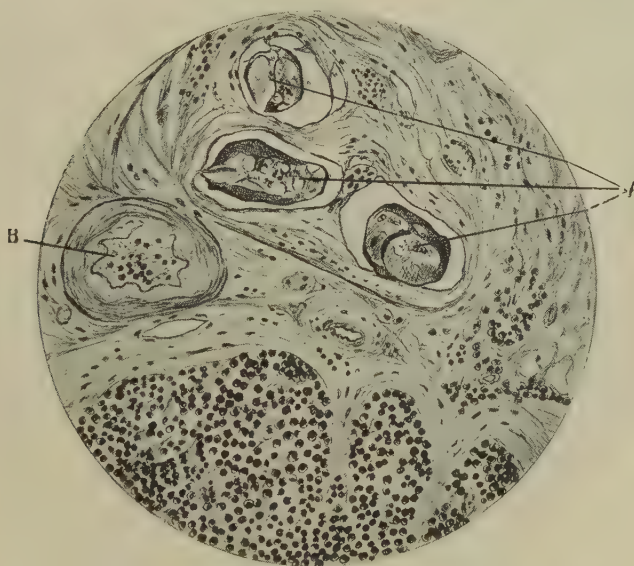


Fig. 124.—Section of a fibrosed lymphatic gland.

A, Portions of a calcified *F. bancrofti*; B, partially occluded lymphatic vessel.

not been definitely and absolutely ascertained for all types of filarial disease. Apparently, in some instances a single worm, or a bunch of worms, may plug the thoracic duct, and act as an embolus or originate a thrombus; or, the worm may give rise to inflammatory thickening of the walls of this vessel, and so lead to obstruction from the consequent stenosis or thrombosis. In other instances the minor lymphatic trunks and the glands may be similarly occluded. (Figs. 124, 125.)

The Editor's work in Fiji has shown that the afferent lymphatic glands situated at some considerable distance from the actual seat

of the filaria worms, for instance the lumbar glands, undergo considerable changes, such as fibrosis, focal necrosis, and giant-cell formation. These changes may be due to the destruction of microfilariae within the gland substance, or to toxins actually excreted by the adult worms.

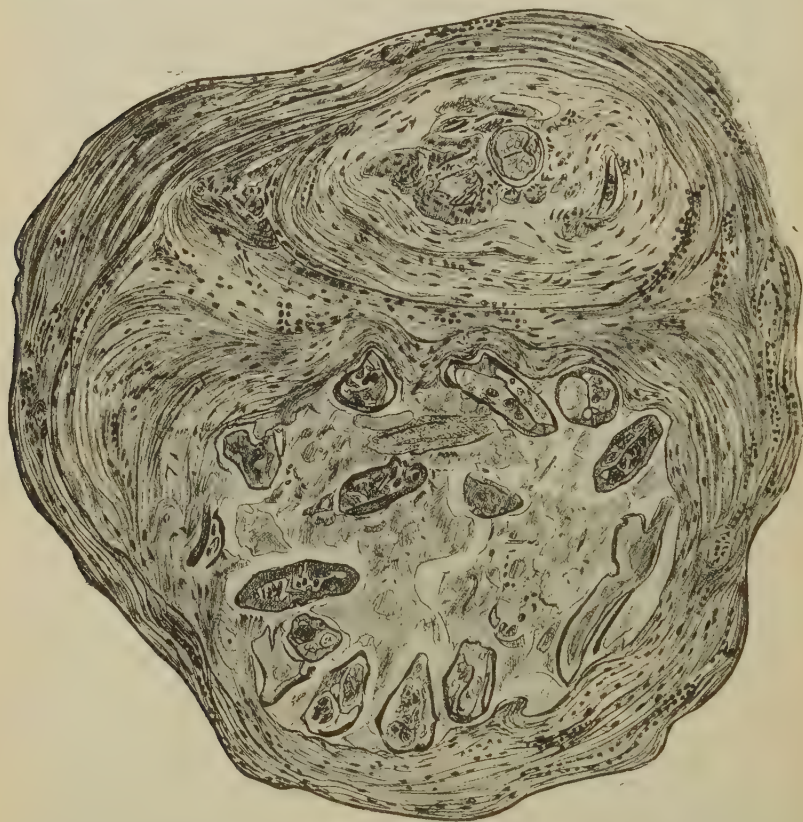


Fig. 125.—Section of a thickened brachial lymphatic containing portions of dead filariæ undergoing disintegration and blocking the lumen of the vessel. Note the large amount of fibrosis.

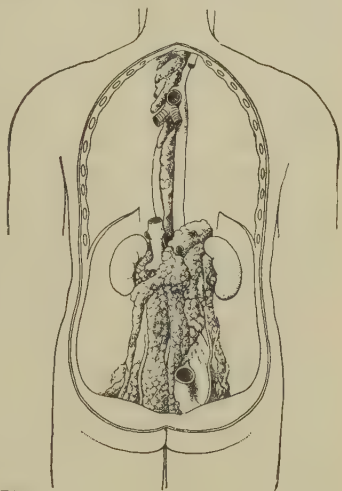
Pathology of lymphatic varix.—In consequence of the rich anastomosis existing between the contiguous lymphatic areas, on filarial obstruction occurring in one of them a compensatory lymphatic circulation is sooner or later established. But before this can be thoroughly effected a rise of lymph-pressure and a dilatation of the lymphatics in the implicated area must take place. This leads to lymphatic varix of different kinds, degrees, and situations. When the seat of filarial obstruction is the thoracic duct, the chyle poured into that vessel can reach the circulation only by a retrograde

movement; this fluid may therefore be forced to traverse in a retrograde way the abdominal and pelvic lymphatics, the lymphatics of the groin, scrotum, and abdominal wall. As a consequence, these vessels, together with the thoracic duct up to the seat of obstruction, become enormously dilated. In dissections of such cases (Fig. 126) the thoracic duct has been found distended to the size of a finger, the abdominal and pelvic lymphatics forming an enormous varix, perhaps a foot in diameter and some inches in thickness, concealing kidneys, bladder, and spermatic cords. In such cases, when one of the vessels of the varix is pricked or ruptures, the contents are found to be white or pinkish. They are not limpid like ordinary lymph. They are chyle, therefore—chyle on its way to enter the circulation by a retrograde compensatory track. When the varix involves the integuments of the scrotum, the result is “lymph scrotum”; when most prominent in the groin, then a condition of glands is produced which Manson called “varicose groin-glands”; when the lymphatics of the bladder or kidneys are affected and rupture from over-distension, then chyluria is the result; when those of the tunica vaginalis rupture, then there is chylous dropsy of that sac—“chylocele”; the same may happen in the peritoneum—chylous ascites. Occasionally varicose lymphatic glands, resembling those frequently encountered in the groins, are found in the axilla. Occasionally, also, limited portions of the lymphatic trunks of the limbs are similarly and temporarily, or more permanently, distended. This, doubtless, is the pathology of all those forms of filarial disease characterized by visible varicosity of lymphatics, with or without lymphorrhagia. It may happen that the obstruction is in some lymphatic tract on the distal side of the entrance of the chyle-bearing vessels into the receptaculum chyli. In this case a rupture of the consequent lymphatic varix will give issue to a limpid lymph unmixed with chyle.

In filarial disease associated with lymphatic varix, microfilariae are generally present in the blood as well as in the contents of the dilated vessels. Sometimes, it is true, the microfilariae are not found. Such cases are probably of long standing; had the microfilariae been looked for at an earlier stage of the disease, they would presumably have been discovered.

The microfilariae have been seen to vanish from the blood-stream by various observers; doubtless this is due to the death of the parent parasite, and is generally associated with an attack of lymphangitis.

Pathology of elephantiasis. *Reasons for regarding elephantiasis as a filarial disease.*—(1) The geographical distribution of *F.*



[7]

Fig. 126. — Dissection of the lymphatics in a case of chyluria, showing the dilated right and left renal lymphatics and the thoracic duct. (*Mackenzie. "Trans. Path. Soc. Lond."*)

bancrofti and that of elephantiasis correspond ; where elephantiasis abounds there the filaria abounds, and vice versa. (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently concur in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum. (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that with rare exceptions the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause.

If the filaria be the cause of tropical elephantiasis, how account for the absence of the embryos from the blood, as is the case in the majority of instances of this disease ? The answer is : Either the disease-producing filariæ have died ; or the lymphatics draining the affected area are so effectually obstructed by the filaria, its products, or its effects, that any microfilariae they may contain, or may have contained, cannot pass along these vessels to enter the circulation. Adult filariæ of both sexes in large numbers may be found in enlarged fibrosed lymphatic glands—epitrochlear, for example—without the presence of the corresponding microfilariae in the blood-stream.

We have already seen that in filarial lymphatic varix the parasites which produced the disease may die, particularly during attacks of lymphangitis ; we have also seen that they may become cretified and may be found in large numbers in this condition or alive in the glands and lymphatic trunks, where, as the Editor has shown, they give rise to giant-cell formation and fibrotic changes of an obstructive nature (Fig. 125).

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis alone does not produce elephantiasis ; this has been proved by ligature of the lymphatic trunk, which results in œdema but not in true elephantoid hypertrophy.

Anderson believes that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection however mild, is able to obtain a foothold, and that

by the changes thus produced the lymph-channels become further occluded.

In these ways one can explain the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease. The latter cannot pass the occluded glands. Very likely the parent worm or worms die at any early stage of the disease, killed by the subsequent lymphangitis, or by the cause which led to premature parturition.

That lymphangitis is not a necessary precursor of *all* cases of elephantiasis may be gathered from a study of elephantiasis of the extremities in temperate climates. Of these a proportion may be ascribed to an inflammation of septic origin affecting the main lymphatic trunks, while others, albeit somewhat rare, supervene without any ascertainable exciting cause.

The subjects of elephantiasis less liable than others to have microfilariae in their blood.—Why should elephantiasis cases have proportionately fewer microfilariae than the non-elephantiasis cases? The answer may be that in the former the existence of elephantiasis implied that a large area of their lymphatic systems was blocked, and the blood could be stocked with microfilariae carried by the lymph from only a relatively small lymphatic area; and that there was therefore a proportionately lesser likelihood of the parent filariae having for their young an unobstructed passage to the blood.

This apparent anomaly is found in other conditions produced by *F. bancrofti*. In Fiji, for instance, the Editor observed that 38·2 per cent. of the cases of elephantiasis he saw harboured microfilariae, while the microfilariae-rate in cases of glandular enlargement, also of filarial origin, was 34·6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19·7 per cent., thus affected had microfilariae in the blood, but that no less than 44·8 per cent. of those with numerous microfilariae showed no obvious sign of disease whatever. The British Guiana Filarial Commission decided that, when present as a simple infection, *F. bancrofti* produces no pathological signs.

SYMPTOMS, DIAGNOSIS, AND TREATMENT OF FILARIAL DISEASES

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *F. bancrofti* are—abscess; lymphangitis; arthritis; synovitis; abscess of hip-joint; varicose groin-glands; varicose axillary glands; lymph scrotum; cutaneous and deep lymphatic varix; orchitis; funiculitis; chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts; chylous dropsy of the tunica vaginalis; chylous ascites; chylous diarrhoea, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariae in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms.

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.¹ Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course, or may be opened; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm itself which has become secondarily infected, but when no such occurrence takes place the defunct filaria becomes cretified.

Lymphangitis and elephantoid fever.—Lymphangitis is a common occurrence in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. When occurring in the limbs the characteristic painful, cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting, and sometimes delirium. After a time the tension of the inflamed integuments may relieve itself by a lymphous discharge from the surface. Usually the attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis), or abdominal lymphatics. When it affects an extensive abdominal varix, symptoms of peritonitis are rapidly developed, and may prove fatal.

Observations by Anderson indicate that a streptococcus is invariably present in these cases.

In the Pacific islands a form of filarial fever is commonly met with in heavily-infected districts unassociated with signs of lymphangitis; in this form there is probably an inflammation of the deep-seated lumbar lymphatics or glands, which are not visible.

¹ Wise and Minett have found filariæ, living or cretified, in the following situations, viz. : pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), the ilio-psoas muscle (4 times), Glisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations have been made by the Editor in Fiji.

Diagnosis.—This fever, usually termed “elephantoid fever,” occurs at varying intervals of weeks and months, or years, in nearly all forms of elephantoid disease. Its tendency to recur, the severe rigor, and the terminal diaphoresis, cause it to be mistaken for ague. In Barbados, where there was until recently no malaria, it is habitually called ague. In Samoa it is known as “mumu fever”; in Fiji as “wanganga.” In the absence of the malaria parasite, there should be no difficulty in arriving at a diagnosis. At one time in India the recurrent fever was believed to depend upon mysterious lunar influences.

Treatment.—The treatment should consist in removing any cause of irritation, in rest, elevation of the affected part, cooling lotions or warm fomentations, mild aperients, opium or morphia to relieve pain, and, if tension is great, pricking or scarifying the swollen area under suitable aseptic conditions. Subsequently the parts, if their position permits, should be elevated and firmly bandaged. Following upon the work of the Editor, Wise, and Rose, suggesting that many of the symptoms of filariasis are of septic origin, Anderson obtained definite amelioration in his cases in British Guiana, and, in some instances, freedom from symptoms for a considerable period, by the injection of staphylococcal or streptococcal vaccines. Detoxicated vaccines gave slightly better results, though in each case the offending organism should, if possible, be determined. The initial dose should be 10 million organisms; three or more injections should be given every third day till the maximum of 50 million is reached.

Varicose groin-glands (Figs. 127, 128).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions coexist in the same individual.

As a rule, the patient is not aware of the existence of these varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both groins, or only one groin; they may affect the inguinal glands alone, or the femoral glands alone, or (and this is generally the case) both sets together.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion;

that though pressure causes them to diminish, they do so slowly ; that there is no sudden dispersion accompanied by gurgling, as in hernia, on taxis being employed ; that they convey a relatively slight or no impulse on coughing ; that they slowly subside on the patient lying down, and slowly return, even if pressure be applied over the saphenous or inguinal openings, on the erect posture being resumed. The cautious use of the hypodermic needle will confirm diagnosis, which may reveal tiny microfilariae, or actually filarial eggs, and the diagnosis would be further strengthened by the co-existence of lymph scrotum, chyluria, or chylous hydrocele, and



Fig. 127.—Varicose groin-glands and chylocele.

the presence of microfilariae in the blood. *Chronic swellings about the groin, cord, testis, and scrotum in patients from the tropics should always be regarded as possibly filarial.*

Treatment.—Unless they give rise to an incapacitating amount of discomfort, and are the seat of frequent attacks of lymphangitis, varicose groin-glands are best left alone. Excision is not always satisfactory, as it may be followed by lymphorrhagia at the seat of the wound, by excessive dilatation of some other part of the implicated lymphatic area, by chyluria, or by elephantiasis in one or both legs.

Similar varicose dilatation of the axillary glands is sometimes, though much more rarely, found. Bancroft designated these varicose axillary and groin glands "helminthoma elastica."

Cutaneous and deeper lymphatic varices.—Occasionally cutaneous lymphatic varices are seen on the surface of the abdomen, on the legs, arms, and probably elsewhere. Filarial lymphangiectasis of the spermatic cord is not uncommon. The contents may be milky and chylous, or straw-coloured and lymphous, according to situation and connexions.

Thickened lymphatic trunks.—In cases of lymphangitis, after the initial swelling and inflammation have subsided, a line of thickening remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved have been found by Maitland, Daniels, and the Editor, and in these cysts coiled-up adult filariæ, sometimes dead, sometimes alive.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the total population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. across, and may form permanent tumours in the groin. On section they have the appearance of an unripe pear, the central portion being fibrotic, and the peripheral glandular. The deep-seated glands—the iliac, lumbar, mesenteric, and mediastinal—may also be enlarged.

On careful dissection, live filariæ or their calcified remains may be demonstrated in the glandular substance. (Figs. 129 and 130.)

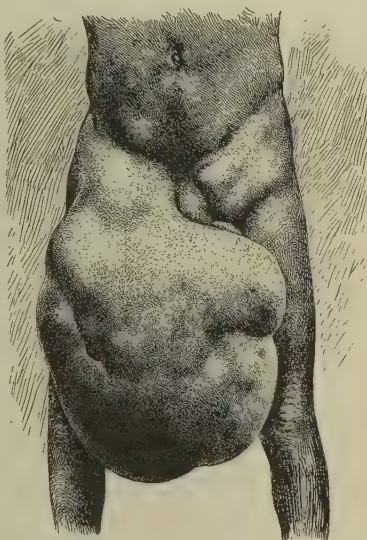


Fig. 128.—Unusually large varicose groin-glands.
(*"Journ. of Trop. Med."*)

Treatment.—Usually it is inadvisable to remove these glands, seeing that, as in the case of varicose groin-glands, an incurable lymphocele might result.



Fig. 129.—Pedunculated groin-glands in a Fijian with double hydrocele. (*Orig.*)

These glands, containing adult ♂ and ♀ filariæ, were removed at operation. No microfilariæ were found in the blood. There were also masses of enlarged glands in right groin.

Lymph scrotum (Fig. 131).—In this disease the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few, or a large number of smaller or larger lymphatic varices which, when pricked or when they rupture spontaneously, discharge large quantities of milky, or sanguineous-looking, or straw-coloured, rapidly coagulating lymph or chyle. In some cases 8 or 10 oz. of this substance will escape from a puncture in the course of an hour or two; it may go on running for many hours on end, soiling the clothes of the

patient and exhausting him. Usually *microfilaria* can be discovered in the lymph so obtained, as well as in the blood of the patient. In a large proportion of cases of lymph scrotum the inguinal and femoral glands, either on one or on both sides, are varicose.

Treatment.—Unless inflammation be a frequent occurrence, or there be frequent and debilitating lymphorrhagia, or unless the disease tend to pass into true elephantiasis, lymph scrotum—kept scrupulously clean, powdered with boracic acid, suspended, and protected—had better be left



Fig. 130.—Pedunculated groin elephantiasis.

(Photo : Dr. C. W. Daniels.)

alone. Should, however, it be deemed expedient, for these or other reasons, to remove the diseased tissues, this can be effected easily. The scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues, and hardly any flap, should be left. Sufficient covering for the testes can be got by dragging on and, if necessary, dissecting up the skin of the thighs, which readily yields and affords ample covering. It is a very common but a very great mistake to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.

In consequence of this violent interference with a large varix, of which

that in the scrotum is but a part, chyluria, or elephantiasis of a leg, may supervene. The patient should be warned of this possibility.

Chyluria.—When a lymphatic varix in the walls of the bladder, or elsewhere in the urinary tract, the consequence of filarial obstruction in the thoracic duct or in the lymphatics of the urinary system, ruptures, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often is the case, it contains blood, the condition is known as hæmato-chyluria.

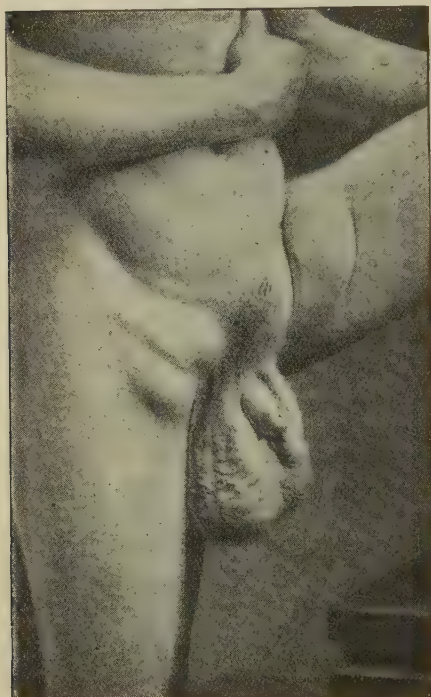


Fig. 131.—Lymph scrotum and varicose groin-glands.

(Photo: Dr. Rennie, Foochow.)

A curious fact about this form of filarial disease is that in the Pacific islands it is practically unknown, though it is frequently met with in filariated subjects in India, China, and North Africa.

This disease frequently appears without warning; usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention,

or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red; sometimes white in the morning, it is reddish in the evening, or vice versa. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Great variety in this respect exists in different cases, and even in the same case from time to time, depending on temporary closure of the rupture in the lymphatic, and also on the nature of the

food.¹ Chyluria is very likely to occur, either for the first time or as a relapse, in pregnancy or after childbirth.

Physical characters of chylous urine.—If chylous urine be passed into a urine-glass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish in colour, is floating about in a milky fluid, the milky appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is formed a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white in colour, in which floats the contracted coagulum. If a little of the sediment be taken up with a pipette and examined with the microscope, it is found to contain red blood-corpuscles, lymphocytes, granular fatty matter, epithelium, and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariæ. The middle layer contains much granular fatty matter; while the upper, cream-like layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariæ, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariæ in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear; the fat may be recovered by decanting and evaporating the ether which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four hour sample of chylous urine contains 1·8–2·6 per cent. of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested with the diet.

Although chyluria is not directly dangerous to life, yet, being prolonged, it gives rise to pronounced anæmia, with depression of spirits and feelings of weakness and debility, and tends to incapacitate the patient for active, vigorous life.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as “filarial lymphuria,” as Low and Wise have suggested. In these cases the abnormal element is lymph, and contains no trace of fat. Albumin is present in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found

¹ The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, and as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics; in these cases the microfilariæ appear in the urine passed during the night-time only.

the lymphatic obstruction located in the kidney lymphatics, which was due to calcification of defunct filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere; that is to say, by resting and elevating the affected part, and thereby diminishing as far as possible the hydrostatic pressure in the distended vessels.

The best results are obtained by sending the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boracic acid, appears to be the best form of treatment; if there is an admixture of blood, styptics may be added, as follows:

R \bar{y} Adrenalin, 1 : 1,000	3 i.
Zinc. sulph.	gr. v.
Lot. acid. bor. ad	5 x.

To be used with an equal quantity of hot water.

Chylous dropsy of the tunica vaginalis, and of the peritoneum; chylous diarrhœa.—Chylous dropsy of the tunica vaginalis is not an unusual occurrence in the tropics. A fluctuating swelling of the tunica vaginalis, which does not transmit light, and which is associated possibly with lymph scrotum, with varicose groin-glands, with chyluria, or with microfilariæ in the blood, would suggest a diagnosis of this condition.

Treatment.—These chyloceles may be treated as ordinary hydroceles, either by aseptic incision or by injection. As a rule, the chylous fluid rapidly coagulates when withdrawn, but occasionally this does not occur, or it may be prevented by drawing the fluid off into a solution of citrate of potash.

If a minute portion of absorbent cotton is dipped into the receptacle, it will slowly fall to the bottom of the fluid. If the cotton is now picked up and placed under a low-power microscope, it will be found that every fibre is beset with multitudes of wriggling microfilariæ entangled by their redundant sheaths; the preparation suggesting the snake-beset Gorgon-head.

Filarial orchitis with effusion into the tunica vaginalis, according to Maitland, is best treated by incision of the tunica vaginalis, turning out any clot that may be found in the sac, and stuffing the latter with iodoform gauze.

Chylous dropsy of the peritoneum and chylous diarrhœa of filarial origin are very rare.

Filarial orchitis, endemic funiculitis, and hydrocele.—The fever attending filarial orchitis—which is usually associated with lymphangitis of the spermatic cord—has been described as a separate disease (“endemic funiculitis”), but it is undoubtedly of filarial origin. It may be attended with inflammation of the scrotum, and, like ordinary elephantoid fever, resemble very closely a malarial attack, for which it may be mistaken. In cases of recurring orchitis of filarial origin with pyrexia, adenitis and rigors, the Editor has demonstrated large numbers of microfilariae in the tunica vaginalis at the commencement of each attack. The aspirated fluid is cloudy, contains a number of polymorph cells, occasionally erythrocytes with sheathed microfilariae as well as others which have cast their sheaths. In these cases the epididymis is enlarged and nodular. In sections it is possible to demonstrate dead and calcified filariae blocking the vasa efferentia and causing extensive fibrotic changes, and it is possible that sterility is a direct result of the invasion of the genital organs by filariae.

Recurrent attacks of filarial orchitis lead sooner or later to *hydrocele*. This condition is extremely common in association with elephantiasis of the scrotum, especially among the Polynesians. The walls of the sac are thickened and contain calcified remains of adult filariae; the fluid is clear, straw-coloured, and usually contains microfilariae or their remains, though, owing to the rapidity with which these embryos die in hydrocele fluid, it does not seem to be a medium particularly favourable to their prolonged existence. These hydroceles should be treated on the ordinary lines.

Septicæmia.—An acute fatal septicæmia due to *Streptococcus longus* is not an infrequent occurrence in subjects infected with *F. bancrofti*. It is suggested that the parent worm living in the lymphatic system damages the lining of the vessels, and thus prepares the ground for any pyogenic organisms which invade the lymph-stream. In damaged lymphatic tissue the streptococcus finds a favourable medium, and enters the blood-stream, with the result that septicæmia is produced.

Filarial synovitis.—Acute synovitis of the knee-joint is one of the filarial diseases. The concurrence of synovitis with filarial invasion is too common to be accidental; fibrotic ankylosis often results. In cases where the hip-joint is affected, removal of the inflamed iliac glands draining the area appears to relieve the condition.

In severe cases the synovitis may even proceed to pus-formation, and a fatal result ensue. Surgical intervention is often indicated.

ELEPHANTIASIS

In certain districts in Cochin about 5 per cent. of the population, in Samoa about every second individual, in Huahine seven-tenths of the adult male population, are affected by this disease. In the Ellice Islands, out of a total population of 3,434, 90 are affected. In many other tropical and subtropical countries elephantiasis, if not so common as in those mentioned, is, nevertheless, very prevalent.

The pathology of the disease has already been considered (p. 548).

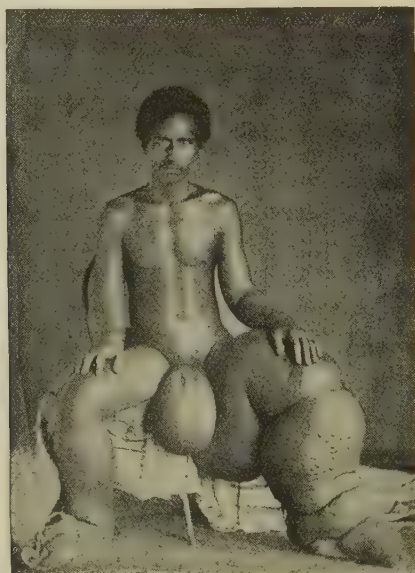


Fig. 132.—Elephantiasis of legs; scrotum and right arm also affected.
(Photo: Dr. Turner, Samoa.)

Parts affected.—In 95 per cent. of the cases the lower extremities—either one or both—alone, or in combination with the scrotum or arms, are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh, may each, or all, be involved. The scrotum is also a common situation for elephantiasis. The arms are more rarely attacked; still more rarely the mammæ, vulva, and circumscribed portions of the integuments of the limbs, trunk, neck, or scalp. In Fiji elephantiasis of the arm is comparatively common; out of 47 cases the arms alone were affected in 10, both arms and legs in 6 cases.

The recurring erysipeltoid attacks.—The disease in any of these situations commences with a rapidly evolved lymphangitis, dermatitis, and cellulitis, accompanied by elephantoid fever.

The lymphatic glands draining the affected area are generally enlarged.

The affected part is greatly increased in bulk. The surface of the skin, in confirmed elephantiasis especially, is rough and coarse; the mouths of the follicles are sometimes unusually distinct; the papillæ and glands are either hypertrophied or atrophied; the hair is coarse and sparse; the nails are rough, thick, and deformed. Around joints the thickened integuments are thrown into folds, the comparatively smooth-sided and deep interlying sulci permitting limited movement. There is no distinct line of demarcation between healthy and diseased skin. The implicated integuments are



Fig. 133.—Plain web-elastic stocking, with foot-piece, for slight degrees of elephantiasis of leg. (*James Woolley & Sons, Manchester.*)

hard, dense, pit but slightly, if at all, on pressure, and cannot be pinched up or freely glided over the deeper parts.

On cutting into the swelling, the derma is found to be dense, fibrous, and enormously hypertrophied. The subjacent connective tissue is increased in bulk, having, especially in the case of the scrotum, a yellowish, blubbery appearance from lymphous infiltration. A large quantity of fluid wells out on division of such tissues.

Elephantiasis of the legs (Fig. 132).—Elephantiasis of the lower extremities is usually, though by no means always, con-



Fig. 134.—Laced form of elastic stocking, with suspenders, adjustable so as to avoid pinching. (*Hospitals & General Contract Co.*)

fined to below the knee. The swelling may attain enormous dimensions and involve the entire extremity, the leg or legs attaining a circumference, in aggravated cases, of several feet.

Treatment.—In the treatment of elephantiasis of the leg the patient should be encouraged to persevere with elastic bandaging, massage, and elevation of the limb. Swellings in the early stages may to some extent be controlled by elastic bandages or stockings. The latter, which should be made to fit the legs accurately, should be of some porous elastic and washable material, such as stockinette. Such a stocking (Fig. 133) should embrace the dorsum



Fig. 135.—Elephantiasis of scrotum; left leg slightly affected.

(Photo : Dr. Turner, Samoa.)

of the foot and should accurately fit the leg to reach above the knee. Difficulty is generally experienced with the upper margin, which extends to the thigh, as it is apt to constrict or nip the limb at this point. The difficulty can be overcome by attaching the suspenders to fasten on to the trousers, or to reach across the shoulders like a pair of braces. To obviate the pressure and discomfort of tight-fitting stockings, and to accommodate the fluctuations in the size of the limb which necessarily take place, these stockings may be made to lace up at the sides (Fig. 134). Ligature of the femoral artery has been practised; it is probably useless, and is certainly not a justifiable method of treatment. Sometimes, in

extreme cases, good results are got from excision of redundant masses of skin, a longitudinal strip of three or four inches in breadth by a foot or more in length being dissected off. Electrolysis and mercury have also been used; one questions their value. During the acute attacks, tension may be relieved by aseptic punctures with a sharp lancet. At all times the limb must be carefully guarded from injury, and shoes and trousers worn. Slight injuries provoke inflammatory recurrences. Wading in water, prolonged standing, violent exercise, and exposure to a hot sun are injurious and should be avoided.

Various *operative* measures have been proposed, though none is entirely satisfactory. *Lanz's operation* aims at deep lymphatic drainage. A longitudinal incision is made through the fascia lata down to the femur, the periosteum of which is stripped and the bone trephined in several places; strips of fascia are then inserted into the openings thus made.

Kondoleon's operation consists also in free incision of the fascia lata and removal of large sections of the aponeurosis; the removal of this tissue assists in the anastomosis of lymph channels and veins.

Medicinal treatment.—Cooke has recently obtained favourable results in early elephantiasis of the legs with "protein-shock" treatment, using intravenous injections of fifty to a hundred million typhoid and paratyphoid organisms.

Elephantiasis of the scrotum (Fig. 135).—Elephantiasis of the scrotum, or "scrotal tumour" as it is sometimes called may attain an enormous size: 10, 15, 20 lb. are common weights for these tumours, and 40 or 50 lb. is by no means uncommon. The largest recorded weight is 224 lb.

Anatomical characters.—These tumours consist of two portions (Fig. 136): first, a dense rind of hypertrophied skin (A, e), thickest towards the lower part and gradually thinning out as it merges above into the sound skin of the pubes, perineum, and thighs; second, enclosed in this rind, a mass of lax, blubbery, dropsical, areolar tissue in which testes, cords, and penis are embedded. The shape of the tumour is more or less pyriform. The upper part, or neck, on transverse section (B) is triangular, the base (B, k) of the triangle being in front, the apex (B, j)—usually somewhat bifid from dragging on the gluteal folds—towards the anus, the sides (B, h) towards the thighs. In the latter situation the skin, though usually more or less diseased, is, from pressure, softer and thinner than elsewhere, tempting the surgeon to utilize it for the formation of flaps—not always a wise proceeding. The penis (A, a, B, f) always lies in the upper and fore part of the neck of the mass; it is firmly attached to the pubes by the suspensory ligament. The sheath of the penis is sometimes especially hypertrophied, in some cases standing out as a sort of twisted ram's-horn-like projection on

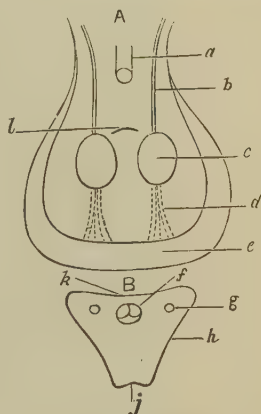


Fig. 136. — Diagram of anatomy of elephantiasis of scrotum. (For references, see text.)

the anterior surface of the tumour; this, however, is unusual. Generally the sheath of the penis is incorporated in the scrotal mass, the prepuce being dragged on and inverted so as to form a long channel leading to the glans penis and opening (A, *l*) half-way down, or even lower, on the face of the tumour. The testes (A, *c*), buried in the central blubbery tissue, usually lie towards the back of the tumour, one on each side—in large tumours generally nearer the lower than the upper part. They are more or less firmly attached to the under-part of the scrotum by the hypertrophied remains of the gubernaculum testis (A, *d*)—a feature to be specially borne in mind by the surgeon. As a rule both testes carry large hydroceles with thickened tunicae vaginales. The spermatic cords also (A, *b*; B, *g*) are thickened and greatly elongated

The arteries which supply these enormous growths are of considerable size; the veins, too, are very large, and, as they permit regurgitation of blood from the trunk, are apt to bleed freely.

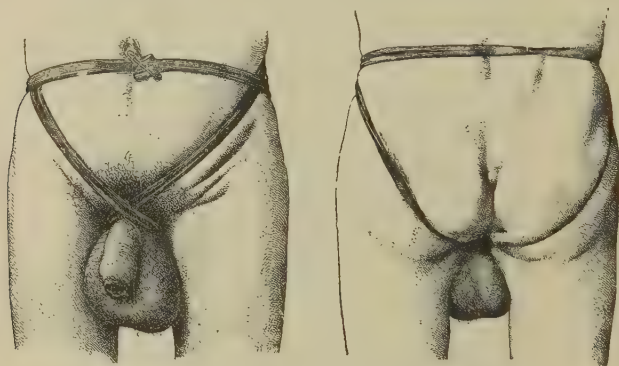


Fig. 137.—Rubber cord in position. (MacLeod.)

Treatment preliminary to operation.—If the tumour is of considerable size the patient should keep his bed for at least a week before operation, the mass being suspended so as to drain it of fluid and blood. It is thus rendered lax, and the operator is enabled to ascertain by palpation the position of the testes and, if such chance to be present, of hernia—a not very unusual complication. The possibility of undescended testes should not be overlooked. The choice of anæsthetic is important: it should be spinal when possible, reinforced with gas and oxygen.

Operation.—The patient should be placed in the lithotomy position. The scrotum should be drawn down as far as possible, and elastic webbing applied over the mass so as to expel the blood; a stout rubber cord is wound round the neck of the tumour, over the pelvis, and firmly secured (Fig. 137). A vertical incision is made commencing in the middle of the symphysis pubis, and extending as far as the aperture leading to the penis. The penis is exposed, separated and the penal artery ligatured. At this point, a sound is passed, and left in to prevent subsequent injury to the urethra. The vertical incision is now continued round the scrotum right round to the back of the perineum, and the scrotum is thus divided into two halves. The

testicles and cords are now separated from the blubbery mass, the hypertrophied gubernacula being divided, surrounded with gauze and placed on one side. At the base of each half of the scrotum clamps are fixed, care being taken that these clamps are well to the proximal side of all diseased tissue. Each half of the scrotum is then cut away, distal to the clamps, and through healthy tissue. Every visible blood-vessel is secured and tied and the clamps very gradually loosened. The skin in the upper and inner aspects of the



Fig. 138.—Elephantiasis of right arm and hand in a Fijian. (*Orig.*)

thigh is undermined as much as necessary and brought together over the testicles. Thiersch skin-grafts may be applied to the penis. It is a good procedure to tie in a catheter till healing has taken place.

Complications which may ensue are severe hæmorrhage, and injury to spermatic cords, urethra or rectum. Postoperative retention of urine is often very troublesome. Stricture of the urethra and the supervention of elephantiasis of a previously unaffected leg have also been recorded.

The mortality from these formidable-looking operations, if they are carefully done, is small, and need not exceed 5 per cent.

Elephantiasis of the arms.—This is comparatively rare. Allowing for the differences between the upper and lower extremities as regards gravitation of fluids, the symptoms and pathology of elephantiasis of the arms are the same as those of elephantiasis of the legs. Beyond the judicious employment of massage and elastic bandaging, little can be done in the way of treatment. (Fig. 138.)

Elephantiasis of the vulva and mammæ.—Elephantiasis of the vulva (Figs. 139, 140) and mammæ (Fig. 141) is still rarer. Where growth has become inconveniently large, the diseased



Fig. 139.—Elephantiasis of labia majora. (After Nuñez.)

tissues should be removed. Instances are on record in which the integuments of the mammæ have become so thickened, heavy, and elongated that the organ has descended to the pubes, and even to the knee. One such tumour weighed 21 lb. after removal. Tumours of the labia or of the clitoris, similarly, may attain a great size—8 or 10 lb., or even more.

Elephantiasis of limited skin areas.—Corney states that pedunculated elephantoid tumours, springing from the groin or from the anterior surface of the thigh, are not uncommon in Fiji. One such tumour which he removed weighed 20 lb. Daniels has seen, both in Fiji and in Demerara, several cases of this description.

Medicinal treatment of filariasis.—It must be confessed that, at present, there is no drug known to be specific for *F. bancrofti*.

Anderson in British Guiana found that certain antimony compounds, such as the colloidal preparation known as "Oscol stibium" (0.5-1 c.c.), given intramuscularly every other day, definitely inhibit the number of circulating microfilariae, and so does sodium-antimony



Fig. 140.—Elephantiasis of vulva.
(Photo: Dr. Walter H. B.
Macdonald.)



Fig. 141.—Elephantiasis of mammae;
left leg and foot also affected.
(Photo: Dr. Davies, Samoa.)

tartrate, if given intravenously in therapeutic doses; but the effect is not permanent. In septic conditions, vaccines are of distinct benefit (p. 551), while intravenous injections of eusol, 40 c.c.,

and liquor hydrarg. perchlor., 3 c.c. of 1 : 1,000 solution, repeated at four-day intervals, are indicated when septicæmia supervenes.

Prophylaxis of filarial disease.—The prevention of filarial disease resolves itself into anti-mosquito measures and protection from mosquito-bite. Unprotected wells, tanks, or stagnant pools must not be permitted in the neighbourhood of dwelling-houses. All vessels used for storing water should be emptied at least once a week. The mosquito-net is indispensable in filarial as well as in malarial countries.

The subjects of filariasis should be regarded as dangers to themselves and to the community, and be compelled to sleep under mosquito-nets.

CHAPTER XXXIII

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES: FILARIASIS (*Concluded*)

II. FILARIASIS DUE TO *LOA LOA*

History and geographical distribution.—The embryonic form, which closely resembles *microfilaria bancrofti*, was described by Manson in 1891; the patient from whom the specimen of blood was derived had formerly had an adult *Loa loa* in his eye. Later, association was established between *L. loa* and the disease known as Calabar swellings, and also between that disease and *microfilaria diurna*.

Loa loa is widely distributed in West Africa from Sierra Leone to Benguela, and is especially common on the Cameroon and on the Ogowe River; its distribution is, however, mainly confined to the coastal plains and follows the course of the Congo and its tributaries to a point about 1500 miles from its mouth (Map VI).

Etiology (Fig. 142).—A minute description of the adult loa is given in the Appendix, p. 779. Here it suffices to say that it is 30 mm. or more in length, the female being, as a rule, considerably longer than her partner. The cuticle is embossed with numerous characteristic protuberances.

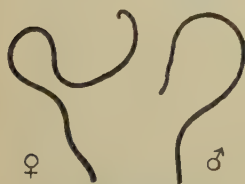


Fig. 142.—*Loa loa*.
Nat. size.

Structure of the embryonic form.—*Microfilaria loa* (= *diurna*) is very similar in size ($298\ \mu$ by $7.5\ \mu$) and structure to *microfilaria bancrofti*. Like the latter, it is enclosed within a "sheath," its tail is pointed, and it has the same V- and tail-spots.

The periodicity is the exact reverse of that of *microfilaria bancrofti*, for the embryos appear in large numbers in the peripheral blood during the daytime and disappear at night. The periodicity is, in fact, *diurnal* (Chart 34).

The respective periodicities are very characteristic—more so, apparently, in the case of *microfilaria loa* than in that of *microfilaria bancrofti*; for whereas by inverting the sleeping habits of a subject of *F. bancrofti* infection it is easy to invert or disturb the periodicity of the microfilariae, this has not been done in the case of *microfilaria loa*, although several experiments have been made.

Life-history.—In early editions of this work Manson called attention to the mangrove fly, *Chrysops dimidiata* (Fig. 345, p. 822), as a possible intermediary, on account of its diurnal and blood-sucking habits and local distribution. This conjecture Leiper, and later Kleine and Connal, have

ascertained to be well founded. Development takes place in the thoracic muscles and fat-body of *C. dimidiata* and *C. silacea*.

It would appear that after the larva has entered the human body, development is very slow, and that probably full maturity is not attained until after several years. In many cases the parasite does not show itself until three, four, or four-and-a-half years after the patient had left the endemic area. In one case the parasite was extracted from the eye thirteen years after the patient had left Africa; in another the worm or worms appeared at irregular intervals during fifteen years. Manifestly it is long-lived. An interesting and suggestive evidence of slow development is that, while the immature active worm is often seen in children, the embryonic form in the blood is found as a rule only in adults, it may be as long as seven years from the time of the original infection.

This slow development of *L. loa* would seem to account for the very frequent failure to find the microfilariae in the blood in cases from which mature parasites have been extracted, a circumstance which has been brought forward

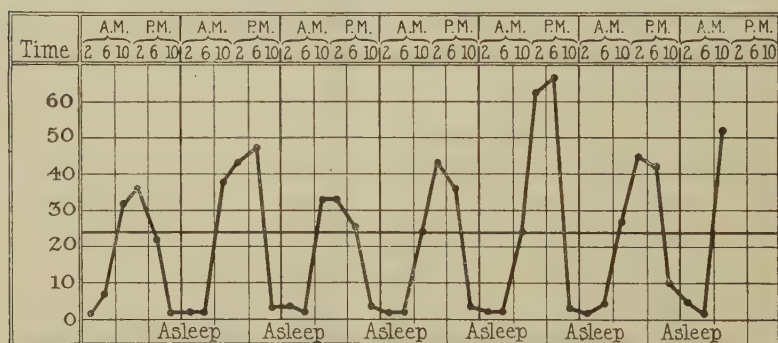


Chart 34.—Diurnal periodicity of microfilaria loa (mf. diurna). (Orig.)

The numbers in the first column are those of the microfilariae per 16 c.mm. of blood.

as an argument against the theory that the diurnal microfilaria is really the offspring of *L. loa*.

As yet it is impossible to estimate accurately the number of adult loas present in any given infection, although in advanced cases some idea of this might be got from the number of microfilariae in the peripheral blood. As a rule, it is safe to conclude that the particular loa that may show itself about the eye or elsewhere is only one of many. Thus, in 1903, Brumpt, at the post-mortem of a negro whose blood contained microfilariae, found in the tissues of the heart five adult worms. Four of these were cretified, but the fifth was alive and contained embryos similar to those in the blood.

Pathology.—As already stated, *L. loa*, during the period of its growth and development in man, makes frequent excursions through the subdermal connective tissues. It has been noticed very often beneath the skin of the fingers, and it has been excised from under the skin of the back, from above the sternum, from the left breast, the lingual frænum, the loose skin of the penis,

the eyelids, the conjunctiva, the anterior chamber of the eye, and also the scalp. The parts most frequently mentioned are the eyes, and, although the worm may attract more attention when in this situation, it does seem as though it had a decided predilection for the eye and its neighbourhood. A patient of Manson's once stated that the average rate at which a loa travelled was about an inch in two minutes. Both he and others have observed that warmth, such as when sitting before a fire, seems to attract them to the surface of the body. Chesterman on the Congo reports finding live adult worms in 10 per cent. of all cases operated upon for hernia, elephantiasis, etc. Cretified worms, too, are frequently encountered.

Symptoms.—As a rule, the migrations of the parasite give rise to no serious inconvenience, but they may cause prickings, itching, creeping sensations, and, occasionally, transient œdematous swellings (Calabar swellings) in various parts of the body. When the parasite appears under the conjunctiva it may cause a considerable amount of irritation and congestion; there may be actual pain even, associated with swelling and inability to use the eye and, perhaps, tumefaction of the eyelids. Should a loa wander into the vicinity of such a situation as the rima glottidis, or the urethra, the consequences might be serious. Great pain is sometimes caused by the wanderings of this parasite in the region of the posterior urethra or the neck of the bladder.

CALABAR SWELLINGS

Under this name Thompstone originally described certain fugitive swellings which are of frequent occurrence in natives and Europeans alike in parts of tropical West Africa. The swellings are about the size of half a goose egg, painless, though somewhat hot both objectively and subjectively, not pitting on pressure, and usually disappearing in about three days. They come suddenly and disappear gradually, and occur in any part of the body. One swelling occurs at a time, but recurs at irregular intervals and, it may be, for many years after the patient has returned to Europe. In some instances the swellings seem to be induced by the rubbing provoked by the irritation accompanying the presence of a loa just under the skin; in other instances they develop spontaneously. When occurring in the hand, or about the forearm, they may give rise to a sensation of powerlessness and soreness, as if the part had received a blow. They never suppurate. (Fig. 143.)

Although in a large proportion of cases *L. loa* embryos cannot be found, in a number of others either the parent worm has

shown itself in the eye or its microfilariæ have been detected in the blood. The latter circumstance, together with the geographical feature of the endemicity of these swellings and their clinical characters, makes it practically certain that they are somehow produced by *L. loa*. Manson believed that the swelling might be caused by the emission of her larvæ by a parent loa into the connective tissue. Possibly the swelling is caused by the death of the parent worm.

The recurrence of Calabar swellings on the arm or leg appear to give rise to induration of the fascia and connective tissue in the vicinity of the tendon-sheaths. In two cases the Editor has

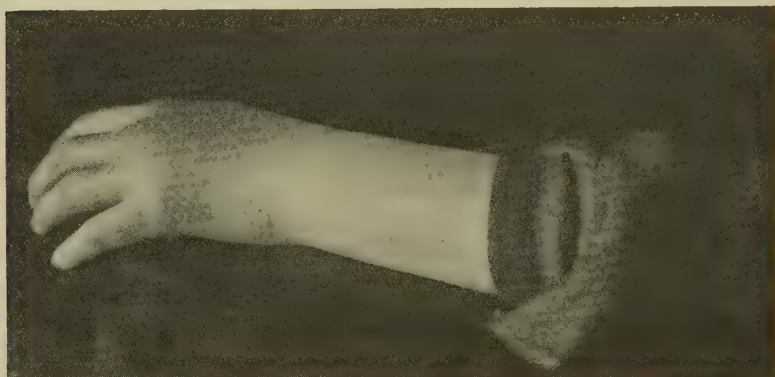


Fig. 143.—Calabar swelling on dorsum of hand in a European lady from the Congo. (Orig.)

observed permanent circular cyst-like swellings which may cause pain on muscular movement. Apparently these swellings are attached to the tendon-sheaths and muscular aponeuroses.

As in infection with *F. bancrofti*, multiple intramuscular abscesses, due to staphylococci or streptococci, and even purulent infection of the hip-joint may be found in association with *Loa loa*.

III. HUMAN ONCHOCERCIASIS

History and geographical distribution.—*Onchocerca volvulus* was originally discovered by a German medical missionary in negroes of the Gold Coast. The contained parasite was named *Filaria volvulus* by Leuckart in 1893. Blanchard, in 1899, demonstrated the parasite as lying in a lymphatic space in a tumour. It occurs sporadically throughout the whole of the Congo basin, but especially on the Oellé, Kibali, and Itimbiri rivers. It has

been observed in Nigeria (Best and Parsons), in the Cameroons (Fülleborn), in Senegal and French Guinea (Clapier), and in Uganda (Cook). (Map VI.)

In 1915 Robles described *O. volvulus* as being of common occurrence in Guatemala. Caldéron (1920) has defined the endemic zones as being in the departments of Sacatapéquez, Escuintla, and Solola, at an altitude of 2,800–3,600 ft. It is suggested that the parasite was imported by negro slaves from Jamaica, though Brumpt regards it as a distinct species—*O. cæcutiens*—mainly on account of its association with a curious punctate keratitis, minor distinctions in the morphology of the male parasite, the predilection of the tumours for the head, and the endemic zone of the disease at an altitude of 600–1,200 metres.

Etiology.—The worms are white in colour and filiform, tapering at both ends. They vary considerably in length, the female, as in all the filariæ, being much the longer (35–40 cm.) At least four males and two females are present in every tumour. The unsheathed embryos measure about 300 μ in length.¹

Life-history.—Embryos, presumably those of *O. volvulus*, have been found in the peripheral circulation by Fülleborn, Simon, Ouzilleau, and Rodenwaldt (Fig. 289, p. 787). The microfilariae occur round the periphery of the tumours, and are ingested by the Ginja-fly (*Simulium damnosum*) in the thoracic muscles of which they undergo a development similar to that of *F. bancrofti* (Blacklock).

Pathology and symptoms.—*O. volvulus* is found in peculiar subcutaneous fibrous tumours, the size of a pea to that of a pigeon's egg. The same patient may present one or several of these tumours. The regions of the body most frequently affected are those in which the peripheral lymphatics converge. Thus the tumours are usually found in the axilla, in the popliteal space, about the elbow, in the suboccipital region, and in the intercostal spaces. In their incipient stages they are the seat of very considerable pain. Periodic recurrences of symptoms are attributable, according to native belief, to the lunar cycle, occurring almost every fifteen days. In the South American form the occipito-frontal and temporal regions were noted to be most usually affected. The tumours are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasites and encloses small cyst-like spaces filled with a greyish viscous substance consisting almost entirely of micro-

¹ Macfie and Corson report that in the Gold Coast natives microfilariae are commonly encountered in sections of the skin. The embryos, they believe, are referable to a new species, *Agamofilaria streptocerca* (see p. 788), distinguishable from those of *O. volvulus*. The presence of this filaria is associated in some with a lichenoid condition of the skin.

filariæ. The position of the adult worms within these tumours is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma; consequently they cannot be extracted unless in fragments. The males lie in the little cyst-like cavities in the tumours, and can be turned out entire. The posterior extremity of the male with its copulating organs, and the anterior extremity of the female with its vaginal opening, are free and contiguous in one of the spaces.

Robles reports that tumours of the scalp may produce epileptiform attacks in Colombia, due to perforation of the cranium by tumours of the periosteum.

Lymphatic enlargement of the scrotum, hydroceles and enlarged testes have been noted by Dyce Sharp in patients infected with *O. volvulus*, while the embryos can be demonstrated in hydrocele fluid, as well as in œdematous lymphatic tissue. On the Congo, Ouzilleau has described elephantiasis of the scrotum and the legs in association with this parasite.

Eye lesions.—In 1918 Pacheco Luna suggested that *O. volvulus*, in its migrations through the body, was responsible for a peculiar form of keratitis punctata commonly found in Guatemala. Caldéron has lately suggested that it produces lesions of the iris and cornea as well. Photophobia, xerosis, and impaired vision result, or the pupil may become obliterated and complete blindness ensue. In the acute stage the eye lesions are associated with erysipelas of the face, neuralgia, and pyrexia. The chronic form is characterized by œdema of the face and a greyish pigmentation of the skin. The skin symptoms have periods of exacerbation every fifteen days. In his recent investigations in South America into this condition, Fülleborn has been unable to confirm the above statements.

Treatment.—In the African form the tumours appear to be painless, and may be removed by excision. In the South American form, removal of the tumours under cocaine anæsthesia is said to be followed by an improvement in the ocular conditions within a week or thereabouts.

IV. DRACONTIASIS

Synonym.—Guinea-worm.

Geographical distribution.—This important parasite, *Dracunculus medinensis*, is found in certain parts of Africa and India, and appears to have been imported into America. In Africa it occurs in the Valley of the Nile, Lake Chad, Bornu, and West Africa; it has been observed in Uganda, but not in the Congo basin. It is also found in Persia, Turkestan, Arabia, and in a very limited part of Brazil (Feira de Santa Anna). Formerly it was

supposed to be endemic in Curaçoa, Demerara, and Surinam. Dracunculus is not equally diffused throughout this extensive area; it tends to special prevalence in limited districts, in some of which it is excessively common. In parts of the Deccan, for example, at certain seasons of the year nearly half the population is affected; and in places on the West Coast of Africa nearly every negro has one or more specimens about him. In Europe, guinea-worm is seen only in natives of, or in recent visitors from, the endemic areas.

Etiology. *The parasite.*—The male worm has only once been found. The female measures about 32·5 cm. to 1 m. 20 cm. in length by 1·5 mm. in diameter. The embryos are somewhat flattened, with a tapering tail, and measure 0·5–0·75 mm. in length by 0·017 mm. in breadth.

Life-history.—The embryos of *D. medinensis* are shed into water and, swimming about actively, enter the body-cavity of a fresh-water crustacean, *Cyclops quadricornis*, or an allied species, in which it develops until a length of 1 mm. is attained. (For details, see Appendix, p. 788.)

Mode of infection.—The metamorphosis of *D. medinensis* in cyclops was discovered by Fedchenko in Turkestan and subsequently confirmed by Manson in England; but, owing to the colder climate of this country, the metamorphosis takes longer to complete—eight or nine weeks, instead of five weeks as in Turkestan. Fedchenko supposed that the cyclops, containing the larvæ of the guinea-worm, on being swallowed by man in drinking-water, was digested, and that the parasite, being then set free, worked its way into the tissues of its new and definitive host.

Later, Leiper showed that when an infected cyclops is transferred to a 0·2-per-cent. solution of hydrochloric acid it is immediately killed, but the larvæ, so far from being destroyed, are aroused to great activity, and eventually escape into the fluid, in which they swim freely. From this he conjectured that under natural conditions man becomes infected through the ingestion of cyclops containing these worms, the gastric juice acting on cyclops and larva in the same way as the hydrochloric acid in his experiment. In order to prove this he fed a monkey on bananas concealing cyclops which had been infected for five weeks, and which contained fully-developed larvæ. Six months later, when the monkey died, five worms were found in its connective tissues, all possessing the anatomical characteristics of *D. medinensis*.¹

The evidence is now fairly complete that the life-span of the female dracunculus extends to about one year, conforming probably to the habits of certain species of cyclops which, under natural conditions, serve as its intermediary host. It is not to be supposed

¹ These experiments have recently been repeated on twenty-two monkeys (*Macacus sinicus*) by Fairley and Glen Liston, who have failed to confirm Leiper's work.

that every species of cyclops is an effective intermediary; if this were the case, guinea-worm infection would have a much wider geographical range.

Pathology and symptoms.—The parasite, on attaining maturity, makes for the legs and feet; these are the parts of the human body most likely, in tropical countries, to come in contact with puddles of water, the medium in which cyclops—the intermediary host—lives. The water-carriers in India are said to be very subject to guinea-worm, which, in their case, is prone to appear on the back—that is, the part of the body against which the water-skin lies when being carried. One might interpret this fact, if fact it be, by suggesting that the mature guinea-worm, conformably to her instinct, seeks out that part of the body most in contact with water, which, in the case of the Indian water-carrier, is his back.

Occasionally the guinea-worm fails to pierce the integument of her host; sometimes she dies before arriving at maturity. In either case she may give rise to abscess; or she may become cretified, and in this condition may be felt, years afterwards, as a hard convoluted cord under the skin, or be discovered only on dissection.

The haunt of the female guinea-worm is the connective tissue of the limbs and trunk. When mature, and prompted by instinct, she proceeds to bore her way through this tissue, travelling downwards. In 85 per cent. of cases she presents in some part of the lower extremities. Occasionally she presents in the scrotum; rarely in the arms (Fig. 144); exceptionally in other parts of the body, or even in the head. In a proportion of cases the appearance of the worm at the surface of the body is preceded by slight fever and urticaria; the onset of the skin eruption is generally at night, before the blister or other localizing signs are noted. Arrived at her destination, the female worm pierces the derma. In consequence of some irritating secretion, a small blister, containing, as a rule, numerous embryos, now forms and elevates the epidermis over the site of the hole in the derma. The irritation due to this act causes a burning sensation and induces the patient to immerse his foot in water. By and by the blister ruptures, disclosing a small superficial erosion $\frac{1}{2}$ – $\frac{3}{4}$ in. in diameter. At the centre of the erosion, which sometimes quickly heals spontaneously, a minute hole, large enough to admit an ordinary probe, is visible. Occasionally, when the blister ruptures, the head of the worm is seen protruding from this hole; as a rule, however, at first the worm does not show. If now we douche the neighbourhood of the ulcer

with a stream of cold water expressed from a sponge and, as the water falls, watch the little hole in the centre of the erosion, we shall see in a few seconds a droplet of fluid—at first clear, later milky—well up through the hole and flow over the surface. Sometimes, instead of this fluid, a small, beautifully pellucid tube, the uterus, about 1 mm. in diameter, is projected through the hole in response to the stimulus of the cold water. Apparently in this act the

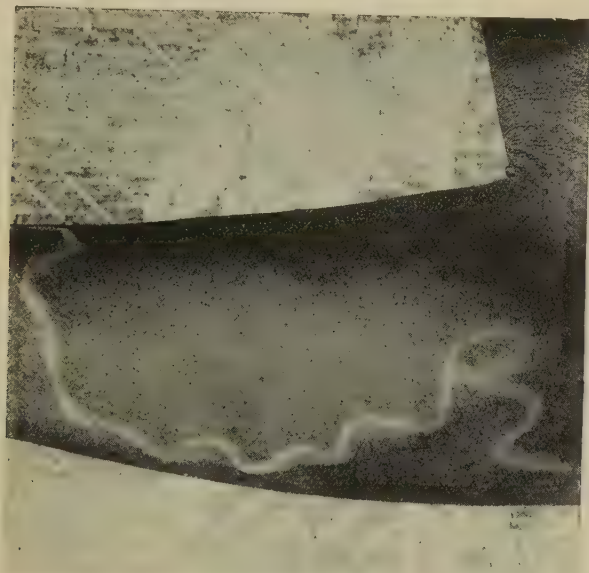


Fig. 144.—Female guinea-worm lying under the skin of the forearm. (*Orig.*)

tissues of the head are exploded in order that the uterus may escape.

When the tube has been extruded an inch or thereabouts, it suddenly fills with an opaque whitish material, ruptures, and collapses, the fluid spreading over the surface of the erosion. If a little of the fluid, either that which has welled up through the hole, or that which has escaped from the ruptured tube, be placed under the microscope, it is seen to contain myriads of dracunculus embryos lying coiled up, almost motionless, with their tails projecting in a very characteristic manner. (Fig. 145.) If now a drop of water be instilled below the cover-glass, the embryos may be observed to unroll themselves, and, in a very short time, to swim about, *more suo*, with great activity. If the douching be repeated after an hour or longer, a further supply of embryos can be obtained; and this can be continued from time to time until the worm has emptied herself. Apparently the cold applied to the

skin of the host stimulates the worm to contract, and thereby force out her uterus, inch by inch, until it is completely extruded.

Should the worm become injured or lacerated while lying in the subcutaneous tissues, severe local reaction may develop. The part becomes extremely painful, inflamed, and oedematous, and cellulitis, due to secondary bacterial infection, may result, caused, as Fairley and Glen Liston have shown, by the downward growth of staphylococci and streptococci from the skin. Arthritis, synovitis, epididymitis, contractions of tendons, and ankylosis of joints have even been known to ensue. In some patients, generalized

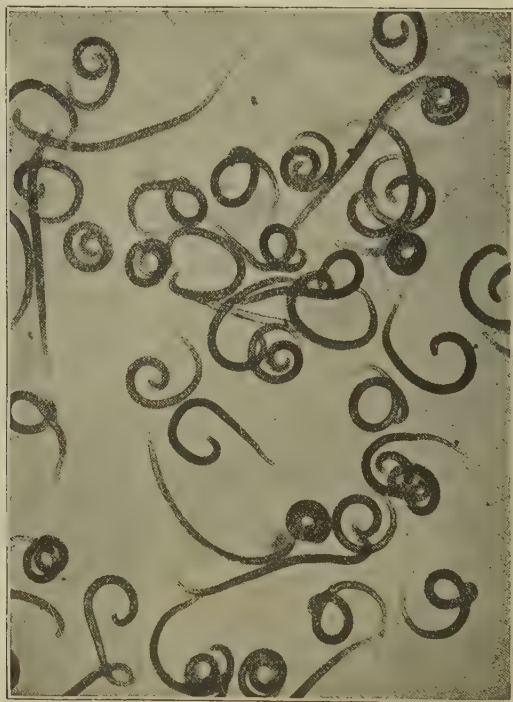


Fig. 145.—Embryos of *D. medinensis*. (Microphoto: Mr. H. B. Bristow.)

systemic symptoms accompany the premonitory urticaria, such as pyrexia, giddiness, dyspnoea, vomiting; and gastro-intestinal symptoms have been noted during the early stages of guinea-worm infection, associated with an increase of eosinophile cells in the blood; this is due to the absorption of a specific toxin, and alarming symptoms may be produced in laboratory animals by intravenous injection of extracts of the adult dracunculus and the embryos.

That the cellulitis associated with guinea-worm is due to the excretion of toxins by the mature parasite has been shown by Fairley and Glen Liston who failed to produce any local or general reaction by subcutaneous injection of the embryos themselves.

Lester from Dar-es-Salaam reports the discovery of an entire guinea-worm found coiled in a hernial sac; it was kept alive in the laboratory for twelve days after removal.

Diagnosis.—This is, as a rule, sufficiently obvious. Generally, if the worms cannot be seen they can be felt underneath the skin. In those cases in which both these methods fail, screening with the X-rays has been found of use; the injection of 2 c.c. of 10-per-cent. collargol into the worm renders it opaque. Effete and calcified worms are easily demonstrated by skiagraphy.

Treatment.—Formerly it was the custom, so soon as a guinea-worm showed herself, to attach the protruding part to a piece of wood and endeavour to wind her out by making a turn or two of this daily. Sometimes these attempts succeeded; just as often the worm snapped under the strain. The consequences of this accident were often disastrous. Myriads of young escaped from the ruptured ends into the tissues, and violent inflammation and fever, followed by abscess and sloughing, ensued; weeks, or months perhaps, elapsed before the unhappy victims of this rough surgery were able to get about. Too often serious contractions and ankylosis from loss of tissue and inflammation, and even death from septic trouble, resulted.

If a guinea-worm be protected from injury, and the part she occupies frequently doused with water, her uterus will be gradually and naturally forced out inch by inch and emptied of embryos. Until this process is completed she resists extraction; possibly the hook at the end of her tail assists her to maintain her hold. When parturition, in from fifteen to twenty days, is completed, the worm is absorbed or tends to emerge spontaneously. A little traction, if practised then, may aid extrusion. Traction, however, must not be employed so long as embryos are being emitted. The completion of parturition can be easily ascertained by the douching experiment already described. When located by X-rays and collargol, the worm may be dissected out (Hudellet).

The parasite may be killed by injecting her, by means of a syringe, with solution of bichloride of mercury, 1 : 1,000; after twenty-four hours, extraction is usually easily effected. If the worm has not shown herself externally, but can be felt coiled up under the skin, the coils should be injected, through several punctures, with a few drops of the same solution. Fairley and Glen Liston advocate aspiration of the blister fluid previous to extraction, followed by precautions to avoid sepsis. They advise actual excision of the worm if lying convoluted in a limited space; failing this, intermittent traction on the worm should be combined with massage. The subcutaneous injection of 9-10 min. of 1 : 1,000 adrenalin hydrochloride immediately relieves the distressing prodromal symptoms from absorption of toxins such as urticaria and asthma.

Fairley and Glen Liston recommend that after the worm has been located by making it prominent and palpable by applications of ice or ethyl chloride to induce contraction of its musculature, two or three small incisions are made across the length of the worm, loops are pulled out with a strabismus hook, cut across, and the pieces withdrawn through these openings and the sinus, the latter being disinfected with a 1 in 30 carbolic solution.

Intravenous injections of tartar emetic appear to exert little or no influence upon the dracunculus.

Peltier and Dominique, however, claim that when mixed with equal parts of an extract of sheep's liver, intravenous injections of 1-per-cent. antimony-tartrate solution become effective. Injections are made every four days, increasing by 1 c.c. up to a maximum of 5 c.c.

Prophylaxis.—From what has been stated with regard to the rôle of cyclops, it is evident that prevention is merely a question of protecting drinking-water from pollution by guinea-worm patients. Leiper has shown that, by raising by a few degrees the temperature of the water in which cyclops are living, these crustaceans are killed. He suggests heating by a portable steam generator the water in wells and water-holes known to be sources of guinea-worm infection. Alcock has found that the addition of a trace of potash to the water is equally effective.

CHAPTER XXXIV

PARASITES OF THE LUNG AND LIVER

I. PARAGONIMIASIS (ENDEMIC HÆMOPTYSIS)

History.—This disease and the characteristic eggs appearing in the sputum of its subjects were described by Baelz and Manson in 1880. Ringer, in 1881, was the first to find the mature parasite, which was afterwards described by Cobbold under the name *Distomum ringeri*; subsequently it was recognized to be closely related to the previously described *Paragonimus westermanii* of the tiger. The main features of its life-history and pathological bearings have been worked out since by Japanese observers. Closely allied species are found in the pig, dog, cat, otter, and ichneumon. (See Appendix, p. 719.)

Geographical distribution.—Paragonimiasis occurs in China, Japan, Korea, Formosa, and the Philippines. In many of the endemic districts a notable percentage of the population is affected. The parasite which gives rise to this peculiar form of blood-spitting has been found in the United States in the cat, in the dog, and in the domesticated hog, but, so far, no cases of the disease in man have been reported from America.

Etiology.—The fluke, *Paragonimus ringeri* (*westermanii*), is reddish-brown in colour, thick and fleshy, oval in shape, and measures 8–20 mm. in length by 5–9 mm. in breadth. Development of the parasite proceeds in the fresh-water snail *Melania*, and thereafter the larva encysts in several species of fresh-water crabs and crayfish. (See Appendix, p. 722.) Man is infected by eating raw or improperly-cooked crabs of which the Koreans are very fond, while the raw juice of crayfish is taken as a medicine for diarrhœa.

Pathology.—On making a section of the lungs in this disease, a larger or smaller number of what are known as “burrows” are discovered scattered about the organ, particularly towards the periphery. These burrows consist of areas, somewhat larger than a filbert, of infiltrated lung tissue in which can be seen a number of tunnels filled with the same material that constitutes the characteristic sputum, and also containing one, two, or more small trematodes. The septa between the tunnels may break down and a considerable cavity be thus produced; and as this occurs in connexion with one of the bronchi, with which the tunnels always communicate, it may give rise to the appearance of a dilated bronchus. One burrow may communicate with another.

When first discovered, it was supposed that *P. ringeri* was

confined to the lungs. We now know that it may affect the liver, peritoneum, testes, intestine, skin, muscle, and brain. In the brain it forms a sort of tunnelled tumour similar to those in the lungs.

Musgrave, in his study of the pathology, points out that the peculiar bluish, cyst-like burrows of the parasite occur in many organs and tissues. The infiltration of the tissues by the eggs produces, especially in the serous membranes, little brownish-red patches sometimes visible to the naked eye. The intestinal mucosa is a common seat of infiltration, which gives rise to inflammatory reaction, ending in ulceration and the appearance of eggs in the fæces. He found no fewer than 100 mature parasites congregated in a psoas abscess.

Symptoms.—The symptoms generally begin so insidiously that it is impossible to fix their onset with accuracy. The subjects of endemic hæmoptysis have a chronic cough, which is usually most urgent in the morning on rising. The fits of coughing eventuate in the expulsion of a peculiar rusty-brown, pneumonic-like sputum. This sputum can be produced at will almost at any time, and often in considerable quantity. In addition to the chronic cough and the tenacious rusty expectoration referred to, the patient is liable to irregular attacks of hæmoptysis. Though usually induced by violent exertion, occasionally such attacks come on without apparent cause. The hæmoptysis may be trifling; on the other hand, it may be so profuse as to threaten life—at all events, to cause intense anæmia. Ogi states that an outstanding physical sign in chronic cases is clubbed fingers.

The sputum.—On placing a minute portion of the viscid, pneumonic-like sputum under the microscope, its peculiar colour is found to be due partly to red blood-corpuscles, partly to a crowd of dark-brown, thick-shelled, operculated eggs (Fig. 146). Besides pus-corpuscles there are seen large numbers of eosinophile cells. Charcot-Leyden crystals are often present. The eggs vary a good deal in size and shape; they are all distinctly oval, have a yellow, smooth, double-outlined shell, and measure from 80 to 100 μ in length by 40 to 60 μ in breadth. If the sputum be shaken up in water, and the water be renewed from time to time, in the course of a month or six weeks—longer or shorter according to temperature—a ciliated miracidium is developed in each egg. When the egg is mature, on placing it on a slide and exercising slight pressure on the cover-glass the operculum will be forced back, and the miracidium will immediately emerge and begin to swim about and gyrate in the water.

Abdominal symptoms in some cases may also be present; they consist of dull abdominal pains and occasional diarrhœa. The abdominal wall feels hard to the touch and is tender; at the same time symptoms of liver cirrhosis, appendicitis, enlargement of the prostate, epididymitis, and adenitis may be present.

Cerebral.—When the disease affects the brain, especially in children, a peculiar form of Jacksonian epilepsy may be a feature for a considerable period, and may eventuate in hemiplegia, aphasia, visual disturbances, pareses or monoplegias of various degrees.

Generalized.—In what is known as generalized paragonimiasis,



Fig. 146.—Eggs of *Paragonimus ringeri* in sputum.

in addition to the symptoms noted above, generalized lymphadenitis, especially affecting the axillary and inguinal groups, is present, associated with cutaneous ulcerations.

Diagnosis.—Diagnosis of endemic hæmoptysis is at once established by the discovery of the characteristic eggs in the almost equally characteristic sputum. Râles and other physical signs of lung consolidation are not usually discoverable. If the intestine or liver is implicated, eggs may appear in the stools.

In the case of one-sided convulsions, or in hemiplegic affections occurring in a native of, or in a visitor from, the countries in which this trematode is endemic, the sputum should be examined on the

chance of discovering evidence of the parasite. Should eggs be found, there is a strong presumption that the cerebral trouble arises from a trematode tumour in the brain.

In the endemic zones of paragonimiasis, even in the absence of eggs in the sputum, Musgrave recommends that this parasite should be suspected in cases of chronic epididymitis, enlargement of the lymph-glands or prostate, liver cirrhosis, and skin ulceration. As some of these conditions are also found in *Schistosoma japonicum* infection, one should be careful to distinguish the operculated eggs of paragonimus from those of the other parasite. It is desirable that the sputum be examined bacteriologically to exclude the tubercle bacillus.

The cutaneous ulcerations have to be distinguished from those of oriental sore.

Yamata reports that severe involvement of the lung in paragonimiasis is readily detected by means of X-rays, but that radiographs of the less extensive infections greatly resemble those of tubercle.

Ando has published a Bordet-Gengou test, using an extract of the body of the adult worm as antigen. This probably, when fully worked out, will constitute an efficient aid to diagnosis in obscure cases.

Treatment.—Hitherto no means of expelling the parasite from the lungs has been discovered. In the case of cerebral paragonimiasis, it might be possible by an operation to remove the parasite and associated tumour, and thus afford a chance of recovery in what has hitherto proved a fatal condition. Kobayashi and Ando have reported encouraging results with emetine, which is said to lessen the sexual activity of the trematodes. The drug is injected intramuscularly in doses of 1.25 c.c. of a 2-per-cent. solution four times daily for five days.

Prophylaxis in this, as in so many other animal-parasite diseases, lies principally in the direction of securing a pure water supply for drinking and bathing purposes, and avoiding all uncooked articles of diet, especially crabs and crayfish, which might be supposed to contain the young parasites. The sputum should be destroyed.

II. CLONORCHIASIS

Geographical distribution.—The trematode responsible for this disease has been found in many Eastern countries, including India, Mauritius, Japan, Korea, Formosa, China, and Tonkin. In South China, Faust and Khaw have recently determined that the fish-raising industry is responsible for the high incidence in Kwan-

tung Province. In the last-named country it appears to be very common. In Central Japan, according to Katsurada, there are certain districts in which it affects from 56 to 67 per cent. of the population, and Léger records finding the eggs in 50 per cent. of the natives of the East Coast of India.

Etiology.—The parasite, *Clonorchis sinensis*, measures 10 to 20 mm. in length by 2 to 5 mm. in breadth; it is oblong, narrow, flat, and somewhat pointed anteriorly, reddish in colour, and nearly transparent. Development outside the human body takes place in two different intermediary hosts—a primary, a mollusc, *Bythinia*; and a secondary, several species of fresh-water fish of the carp family. For further details, see Appendix, p. 716.

Pathology.—*C. sinensis* inhabits the bile-ducts. It thickens the walls

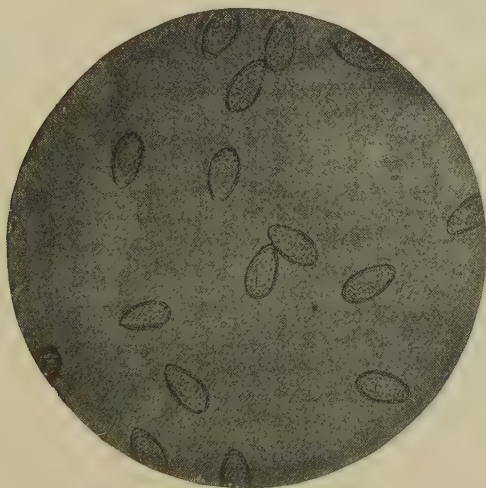


Fig. 147.—Eggs of *Clonorchis sinensis* in fæces. $\times 250$.
(Microphoto: Dr. John Bell.)

of the biliary canals and expands them in places into cavities and diverticula as large as filberts. In these cavities vast numbers of parasites may be found. The diverticula communicate with the bile-ducts, along which the eggs of the parasites, and sometimes the parasites themselves, escape into the intestine. The affected liver is enlarged as a whole, although the tissue in the immediate neighbourhood of the diseased bile-ducts is atrophied. The spleen, also, may be hypertrophied and the intestine in a condition of chronic catarrh. Some instances are recorded of the presence of this trematode in the pancreatic ducts, in the duodenum, and in the stomach, and of the complication of ascites, and even of anasarca.

This parasite, which for long was supposed to be practically innocuous, is now held to be the cause of a serious disease of the liver, which may terminate fatally; indeed, there can be no doubt of this when one considers that

in some of the cases recorded several thousand parasites were present. Sambuc and Baujeau counted 21,000 at one autopsy, and reckoned the total weight of the parasites at 300 gr.

When the infection is severe the liver becomes enlarged, and chronic diarrhoea, with recurring attacks of jaundice, sets in. Later, anasarca appears, and gradually a cachexia, resembling that of sheep-rot, is established, which, in the course of several years, may prove fatal.

Diagnosis.—It would be well to bear in mind this and other parasites in approaching the diagnosis of obscure hepatic disease associated with diarrhoea and jaundice in patients from the East. The discovery of the eggs (Fig. 147) in the stools should guide to a correct diagnosis.

Treatment.—So far, no specific treatment has been found. The patient should be removed to a non-infected area and given nourishing food. Recently, salol has been reported as beneficial in the analogous liver-fluke disease of sheep.

Faust has found that in experimental cats, gentian-violet administration *per os* after preliminary stimulation of ovulation causes death of the fluke for which this dye appears to have a special affinity. About 80 mg. per kilo weight was found to be the correct dosage. Unfortunately this drug appears to be toxic to the host. This work, however, opens up an important line of clinical research.

Prophylaxis.—Manifestly, the Japanese habit of eating raw fish is to be deprecated. Animals and men harbouring the parasite should be prevented from fouling water, whether used for drinking or bathing, or for agricultural purposes.

CHAPTER XXXV

INTESTINAL PARASITES

I. ASCARIASIS

Symptoms.—In many instances the ascaris (*A. lumbricoides*) (see p. 757) gives rise to no very noticeable symptom; in other instances it is to be credited with a number of ill-defined gastric and perhaps nervous troubles—capricious appetite, foul breath, restless sleep, peevishness, vague abdominal pains, nausea, and so forth. It may cause urticaria of a most pronounced type. Sometimes the worms get into the stomach and are vomited, their appearance giving rise to no inconsiderable alarm. They may even creep up the œsophagus and into the mouth, or out by the nostrils. Cases are on record in which they caused suffocation by wandering into the rima glottidis. When aggregated into masses in the intestines they may cause a volvulus, and even intestinal obstruction. They have been known to enter the pancreatic ducts and also the bile-ducts and give rise to jaundice; to penetrate the intestinal wall and escape into the peritoneum, causing peritonitis; or to burrow into the abdominal walls and cause abscess. They may invade the lumen of the appendix and cause appendicitis, and their eggs may occur in profusion in this situation. There is good evidence that absorption of the toxins given off by ascaris may lead to asthma, and it has even been suggested that this may be the exciting cause of the nephritis which is so prevalent in British Guiana and the West Indies. It is possible that the larval stages in the lung capillaries may give rise to pneumonic symptoms.

Diagnosis.—It is well, when puzzled over some obscure dyspeptic condition in tropical patients, to bear the ascaris in mind. If, for some reason, it is undesirable to give santonin diagnostically, the stools ought first to be examined with the microscope. If eggs (Fig. 148) are found, a dose or two of santonin may clear up the diagnosis and cure the patient; if no eggs are found, the drug may be withheld and the idea of ascarides abandoned. The toxic symptoms produced by ascaris infection are probably attributable to a substance known as *ascaron*, a mixture of albumoses and peptones, isolated by Shinamura and Fujii.

Treatment.—The ascaris is readily expelled by a few grains of santonin. The dose is from $\frac{1}{2}$ to 1 gr. for a child, 3 to 5 gr. for an adult. A good method of giving the drug is to prescribe three such doses on successive nights, the first and the last dose to be followed by castor oil next morning. Patients, or mothers, ought to be warned about the peculiar effect santonin has on the urine, and sometimes on the vision.

As a routine vermicide, oil of chenopodium, 0.5 c.c. put up in capsules and given on three occasions, is, according to Darling and Barber, as efficacious as santonin; it has the advantage, too, of being specific for the ancylostome and tænia. The parasites may also be removed by means of carbon tetrachloride, given in

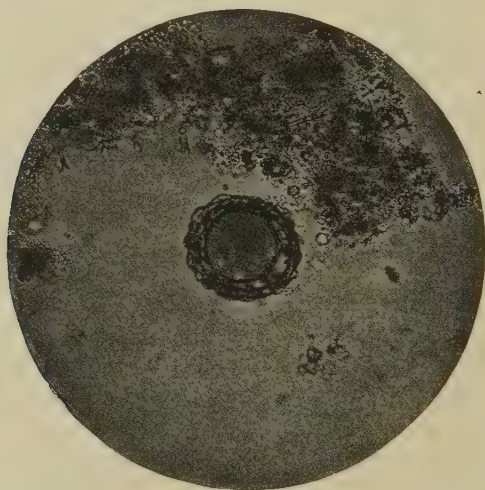


Fig. 148.—Egg of *A. lumbricoides*. $\times 250$.
(Microphoto: Dr. J. Bell.)

capsules in 3-c.c. doses; the drug anæsthetizes the parasites, and in this condition they are removed by subsequent purgation or by enema. This treatment is very effective and no special preparation of the patient is necessary.

Reed and others have recently reported that the action of carbon tetrachloride is increased by the addition of oil of chenopodium; a mixture of 1 drachm of carbon tetrachloride with 1 c.c. of oil of chenopodium should be dissolved in $\frac{1}{2}$ oz. of liquid paraffin and given after a preliminary purge.

Yatren, 4 gr. in pill form, in doses of six pills daily for three

days, has recently been shown to be effective in expelling ascaris from the bowel when other forms of treatment have failed.

II. ANCYLOSTOMIASIS ¹

Synonyms.—Uncinariasis; Hookworm Disease; Egyptian Chlorosis.

Definition.—A disease in its more pronounced forms characterized by great anæmia, debility, and cardiac incompetence, due to the absorption of the toxins of *Ancylostoma duodenale* and *Necator americanus*, nematodes which inhabit the small intestine, and may be sometimes present in enormous numbers. The ancylostome, in many tropical countries, on account of the dangerous cachexia—ancylostomiasis—to which it gives rise, amounts to a positive curse.

History.—The worm, now known as *Ancylostoma duodenale*, was first recognized by Dubini in 1838, and in 1843 he published a detailed account of it, but apparently did not recognize its pathogenic importance. Bilharz (1853) and Griesinger (1854) connected the parasite with the extremely severe chlorosis prevalent in Egypt, but it was not until the very fatal epidemic of anæmia among the miners in the St. Gothard Tunnel (in 1880) had called the attention of European observers to the subject that the importance of this parasite as a pathogenic agent began to be properly apprehended.

Geographical distribution.—The ancylostome has been found so widely diffused that it may be said to occur in all tropical and subtropical countries. It occurs in Belgium, and was found by Haldane to be the cause of an epidemic of severe anæmia in a Cornish mine. In northern countries it is rare; but it is abundantly present in the south of Europe, and in the tropical and subtropical regions of Asia and America. It is especially prevalent in Siam, in South China, and Malaya. In India, Ceylon, and the East Indies it is a source of grave disability in plantations, mines, etc. It occurs abundantly on most of the Pacific islands, and exists in North and South Queensland and in Egypt.

Etiology. (Fig. 149.)—The normal habitat of *A. duodenale* is the small intestine of man, and particularly the jejunum; less so the duodenum, rarely the ileum or lower reaches of the alimentary canal; very occasionally it is found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, from the blood of which it obtains a plentiful supply of nourishment. It is supposed to shift its hold from time to time, the abandoned bite continuing to ooze blood for a



Fig. 149.—*Ancylostoma duodenale*.

Nat. size.

(Dubini.)

a, Male; b, female.

¹ A complete bibliography on this disease has been published in a volume by the Rockefeller Foundation International Health Board. Publication No. 11.

short period. It is said to be very prodigal of the blood it imbibes, the red corpuscles passing through its alimentary canal unchanged, and the plasma alone being utilized.

The male and female ancylostomes—present generally in the proportion of one of the former to three of the latter—do not differ so much in size as is the case with many of the other nematodes. The male (Fig. 149, *a*) measures 8–11 mm. in length by 0·4–0·5 mm. in breadth; the female (Fig. 149, *b*) 10–13 mm. in length by 0·6 mm. in breadth.

Necator americanus closely resembles *A. duodenale*, but is shorter and more slender (see Appendix, p. 761). At first it was thought to be confined to the American continent, but it has been found by Looss and others in pygmies from Central Africa, and by others again in Rhodesia, India, Ceylon, Fiji, the Philippines, and elsewhere. Near Darjeeling in India it is found as a pure infection (Lane), whilst in Egypt *A. duodenale* occurs alone.

Reproduction and mode of infection.—The female ancylostomes produce a prodigious and never-ending stream of eggs (Fig. 150, *A*), which pass out in the fæces. In the body of the host the development of the embryo does not advance very far; but on leaving the human



Fig. 150.—Egg and embryo of *A. duodenale*. $\times 250$.

(Microphotos: Dr. J. Bell.)

A, Egg; B, developing embryo in egg; C, embryo escaping from egg.

host it proceeds, in suitable circumstances, so rapidly in the egg that in one or two days a rhabditiform embryo is born. This minute organism (Fig. 150, B, C) is very active, voraciously devouring what organic matter it can find and, for a week, grows rapidly and moults twice. After the second moulting it passes into a torpid condition, in which it ceases to eat, and growth is suspended. In this state it may live for weeks or months, moving about more or less languidly in muddy water, in mud, or in damp earth, but it is rapidly killed by drying. It is said that it may also encyst on blades of grass. Cort and others have shown that the larvæ lose their sheaths while living in the soil, and continue to exist in the unsheathed state. Arrived in its final host, after moulting again at the end of five weeks it acquires sexual characters and the permanent adult form.

Looss has shown that the parasites reach the intestinal canal by a definite route, by boring their way through the skin. From the subcutaneous tissue they enter the blood-vessels and lymphatics, and by this channel are passively transferred to the lungs. Here they leave the capillaries, enter the air-vesicles, and thence along the bronchi and trachea pass into the œsophagus, and so to the stomach. It has been conjectured that during this passage the larva acquires the power of resisting the action of the gastric juice.

The duration of the life of *A. duodenale* in the intestine has not been determined; some state it in months, others in years (Sonsino)—one to three. On account of liability to reinfection, this point—an important one as affecting prognosis—is difficult to determine.

The exact number of ancylostomes necessary to produce symptoms of disease has exercised much attention. Some consider that 100 worms are necessary to produce pathogenic effects and that 500 to 1,000 worms must be present for at least six months to produce well-marked hookworm disease. Others believe that very few ancylostomes, such as ten or so, may affect the general health and working powers.

According to Lane, the egg-laying capacity of a single female ancylostome is about 30 eggs per c.c. content of fæces per diem.

Pathology.—As already mentioned, the bodies of the victims of ancylostomiasis are not wasted; on the contrary, there is plenty of fat in the usual situations. The appearance of plumpness is further increased by a greater or lesser amount of general œdema. There may be effusions in one or more of the serous cavities. All the organs are anæmic. The heart is dilated and flabby, its muscular tissue being in a state of pronounced fatty degeneration. The liver also is fatty, and so are the kidneys.

If the post-mortem examination be made within an hour or two of death, the ancylostomes, in numbers ranging from a few dozens up to many hundreds, will be found still attached by their mouths to the mucous surfaces of the lower part of the duodenum, of the jejunum, and perhaps of the upper part of the ileum; but if the examination has been delayed for some hours the parasites will have loosed their hold, and are then to be found lying in the mucus coating the inner surface of the bowel. Many small extravasations of blood—some fresh, others of long standing—are seen in the mucous membrane, a minute wound in the centre of each extravasation representing the point at which a parasite had been attached. Sometimes blood-filled cavities, as large as filberts, are found in the mucosa: each cavity enclosing one or

two worms and, probably, communicating by means of a small hole with the interior of the intestine. Old extravasations are indicated by punctiform pigmentation. There may be evidence, in the shape of vesiculations and thickening of the mucosa, of a greater or lesser degree of catarrh. Occasionally, streaks or large clots of blood are found in the lumen of the bowel.

Microscopical examination of the liver and kidneys shows the presence, within the cells of the parenchyma, of grains of yellow pigment having the reactions of hæmatoidin—indicating an intravascular blood destruction such as occurs in pernicious anæmia and other diseases of which excessive hæmolysis is a feature. On this account, and also because he found granules of a ferrous nature in the liver-cells, Daniels concluded that the anæmia in ancylostomiasis is, in a measure, the result of blood destruction within the vessels by some toxic substance produced by the parasite and absorbed from the bowel. These results have not been confirmed by all other observers.

Symptoms.—It is not in every instance in which the ancylostome is present that consequences so serious ensue. There may be dozens of ancylostomes in the intestine without any appreciable anæmia, or, indeed, symptoms of any description whatsoever. Grave symptoms are the exception. One must be careful, therefore, to avoid concluding that the ancylostome is the cause of every pathological condition with which it may chance to concur.

On the other hand, many inhabitants of tropical and subtropical countries are in a state of chronic starvation. Living on coarse, bulky, innutritious food, they are prone to dilatation of the stomach and dyspeptic troubles. In such, any additional cause of malnutrition, as a swarm of ancylostomes, and a daily though perhaps small loss of blood, may be sufficient to turn the scale against them. In those countries, as elsewhere, there are many who live just on the borderland between health and disease; to such the ancylostome may prove “the last straw that breaks the camel’s back.”

It may be that in some persons with special susceptibility a toxin developed by the parasite produces a special type of anæmia, as in certain cases of *Dibothriocephalus latus* infection.

It is evident that as a complication of typhoid, of kidney disease, of dysentery, of malaria, in fact of any chronic or exhausting disease, the importance of this anæmia-producing parasite cannot be ignored.

The practitioner in the tropics, therefore, must be constantly on the look-out, in all cases of anæmia, of dyspepsia, and of debili-

tated conditions generally, for the ancylostome. He must bear in mind that this parasite, as will be presently pointed out, if permitted to remain in the intestine for a length of time, may be the cause not only of remediable anæmia, but of irremediable anæmia-produced degenerations of various organs. On this account, also, its early recognition becomes a matter of the first importance. In native women it frequently causes abortion and interferes with lactation.

Further, ancylostomiasis is an important disease from the standpoint of the employer of native labour. The invaliding and inefficiency which it causes among coolies, not to mention the deaths, are often financially a serious matter to the planter and the mineowner. To them any wisely directed expense or trouble undertaken for the treatment and control of this helminthiasis will be abundantly repaid by the increased efficiency of the labourer.

The essential symptoms of ancylostomiasis are those of a progressive anæmia—an anæmia which is generally associated with dyspeptic trouble, but which, in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serous effusions and fatty degeneration of the heart ensue, and death may occur from syncope or from intercurrent complication.

One of the earliest symptoms of an extensive ancylostome invasion is pain or uneasiness in the epigastrium. This is generally increased by pressure, but for the time may be relieved by food. The appetite, sometimes defective, is more often ravenous, though its gratification is apt to give rise to dyspeptic trouble of various kinds—to colic, to borborygmus, and perhaps to diarrhœa of imperfectly digested food. Constipation may be present in some instances, irregularity of the bowels in others. The taste may be perverted, some patients exhibiting and persistently gratifying an unnatural craving for such things as earth, mud, or lime—what is called *pica* or *geophagy*. The stools sometimes, though rarely, have a reddish-brown tinge from admixture of half-digested blood. Sometimes they may contain small flakes of blood-tinged mucus. Pure blood is seldom passed; and an extensive hæmorrhage, unless there be concurrent colitis, is rare, although, post mortem, considerable quantities may be found in the small intestine. Fever of an irregular, intermitting, or even a subcontinued type is common. On the other hand, the temperature may be constantly subnormal. Or these conditions may alternate. After a longer or shorter time, symptoms of profound anæmia gradually disclose themselves. The mucous surfaces and the skin become pallid, the face is puffy, and the feet and ankles are swollen. All the

subjective symptoms of a definite anæmia now become more and more apparent; there are lassitude, breathlessness, palpitations, tinnitus, vertigo, dimness of sight, mental apathy and depression, liability to syncope, etc. The circulation is irritable, and hæmic bruits can be heard over the heart and larger blood-vessels. Ophthalmoscopic examination may reveal retinal hæmorrhages.

From some of these symptoms, were it not that with the advancing anæmia there is no loss of weight, one might be led to suspect the possibility of tuberculous or cancerous disease, or of Bright's disease. So far from losing weight, the patient may appear quite plump; and though hæmocyto-metric estimates testify to a slow and steady fall in the corpuscular richness of the blood until the lowest limit compatible with life is reached, there is no true poikilocytosis as in idiopathic pernicious anæmia, no excessive leucocytosis as in leucocythæmia, and not necessarily any enlargement of lymphatic glands, liver, or spleen. There is generally a marked eosinophilia of about 7-14 per cent., though in rapidly fatal cases these cells tend to disappear. The depression in the hæmoglobin value of the corpuscles is considerably greater than the fall in their number.

The rate of progress is very different in different cases. In some a high degree of anæmia may be attained, and even a fatal issue, within a few weeks or months of the appearance of the first symptoms. Such rapid cases are rare; more frequently the disease is an exceedingly chronic one, ebbing and flowing, or slowly progressing, through a long series of years. Acute cases develop terminal diarrhœa with passage of much mucus and, occasionally, blood. These cases are apt to be mistaken for various forms of dysentery.

Should serious ancylostomiasis occur before puberty, the growth and development are apt to be delayed and stunted (Fig. 151).

There appears to be some reason for the belief that after generations of exposure to this infection a certain degree of tolerance is attained.

According to Darling, a given number of *A. duodenale* produces a greater degree of anæmia than an equal number of *N. americanus*. It is estimated that twelve worms are required to cause a loss of 1 per cent. of hæmoglobin.

It is not surprising that the severe nutritional changes associated with ancylostomiasis affect the mental powers of an afflicted population. Prolonged exposure to ancylostomiasis in the European has led to the production of a race known as the "mean white," stunted both in mental and in physical capacity. In

Jamaica, in districts where the whole population suffers from ancylostomiasis, not only are the people intensely indolent, but are also predisposed, on this account it is said, to larceny and other crimes.

Diagnosis.—Provided its presence be suspected, ancylostomiasis is easily diagnosed. In tropical countries, in patients coming from tropical countries, and in miners who work in very warm mines in cooler climates, anæmia with concurrent eosinophilia should always suggest a microscopical examination of the fæces. (See Appendix, p. 876.) If the eggs of *A. duodenale* or of *N. americanus* are discovered, and no other reason for the anæmia is made out, the presumption is that one or the other of these parasites is responsible; at all events, no harm is likely to result from treatment based on this supposition. On the other hand, if no eggs are found it must not be concluded that the case is not one of ancylostomiasis; for it sometimes happens that, in the later stages of the disease, symptoms will persist although the parasites which caused them in the first instance have disappeared spontaneously, or have been got rid of by treatment. The usual method of diagnosis by microscopic examination of stools for eggs does not convey a quantitative idea of the severity of the infection. The grade of infection runs from one to a thousand or more worms. Diagnosis by means of a vermifuge is much the most satisfactory method; for instance, according to Darling, where the microscopic examination revealed a 75-per-cent. infection of those examined, diagnosis by vermifuge revealed an incidence of 97 to 100 per cent. The diagnosis by means of eggs has been made much more accurate



Fig. 151.—Ancylostomiasis in a South American Indian boy, showing stunted growth, characteristic facies, and protuberant abdomen. (By permission of the Rockefeller Foundation.)

by the recent method of Clayton Lane, known as the floatation concentration technique (*see* p. 876). It is said that in the majority of cases of ancylostomiasis a positive test of occult blood in the fæces is obtained (*see* p. 874), and Charcot-Leyden crystals are frequently found.

Treatment.—*Thymol* was introduced by Bozzolo in 1880. Before its administration the patient should be put on liquid diet for a day, and have the bowels well cleared out by a saline aperient. In the morning, and following the action of the aperient, three 20-gr. doses of well-triturated thymol, in cachets, in capsules, or in emulsion, are given on an empty stomach at intervals of an hour. If the bowels do not open spontaneously within four or five hours of the last dose, an aperient should be given. Usually, by this treatment many ancylostomes are expelled and may be found in the motions. One such course of thymol may suffice; but it is well, after a week has elapsed, again to examine the stools microscopically, and, if it be found that eggs are still being passed, to repeat the course of thymol once, or oftener.

Certain precautions have to be observed in employing this drug. In some cases, after the exhibition of thymol the urine on standing becomes dusky, almost black, and reduces Fehling on prolonged boiling; this is probably due to hydroquinone. At times thymol gives rise to a very unpleasant form of intoxication—vertigo, excitement, etc. It is advisable, therefore, for the patient, while taking the drug, to keep his bed, and to lie down for several hours after the last dose. Thymol is very insoluble in water, and is consequently, in ordinary circumstances, not readily absorbed in poisonous quantities; should, however, the patient, while thymol is present in the stomach, partake of any alcoholic drink, there is considerable risk of his being poisoned. Alcohol, ether, glycerin, turpentine, chloroform, and oils are all solvents of thymol, and must therefore be avoided when this drug is being exhibited.

Thymol is best given in rice-paper cachets; the addition of an equal quantity of sodium bicarbonate or lactose aids the solution and absorption of the drug, which otherwise is apt to pass through unchanged.

Without careful preparation by rest and judicious feeding thymol must on no account be used in advanced cases of ancylostomiasis, or where prostration is extreme. It is contraindicated in gastritis, dysentery, nephritis, and active heart disease.

Oil of chenopodium is reported to be more efficacious than thymol, and less unpleasant to take, with the additional advantage of being slightly more powerful, and of being toxic to helminths other than the ancylostome. The maximum individual dose is 17 min. (1 c.c.). After light diet and a dose of salts (mag. sulph.), 1 oz. at 6 p.m., it may be given on the following morning in three gelatin capsules, each containing 8½ min. (0.5 c.c.) of the essential oil, at two-hourly intervals, followed by ½ to 1 oz. of magnesium sulphate in three hours' time: castor oil in 2–4-drachm doses is also recommended, and may, if necessary, be repeated. Toxic symptoms produced by an overdose are epigastric pain, colic, nausea, vomiting, general formication, an almost intolerable ting-

ling of the soles of the feet, delirium, coma and convulsions. Considerable confusion has existed, not only as to the exact therapeutic dosage of chenopodium, but also as to its chemical composition. It has been stated that on keeping, the drug loses its efficacy, and becomes non-toxic. The active principle is "ascari-dol," of which test-samples produced by Burroughs Wellcome and Co. contain 90 per cent. As a result of its action 90 per cent. of the ancylostomes are removed. After a pause of fourteen days the treatment may be repeated two or three times.

The dose should be carefully and correspondingly reduced for children, to whom it is best given dropped on sugar.

Oil of chenopodium is equally efficacious for *ascaris* and *Strongyloides stercoralis*.

Carbon tetrachloride (*tetraform*) was introduced by Hall as a vermifuge, and is suitable for mass treatment in a hookworm campaign. The drug is closely allied to chloroform and was formerly employed as an anæsthetic. Its toxic effects¹ are usually considered slight, but if given in large doses it is apt partially to anæsthetize the patients. Carbon tetrachloride is said to exert a selective action on the females of *N. americanus*. The dose for an adult is 3 c.c. (or 1 dr.) taken in hard gelatin-coated capsules each containing 30 min., subsequently to an eighteen-hour fast without previous purgation. Hall reports that in a series of therapeutic tests on coolies in Fiji, 98 per cent. of the ancylostomes were removed by a single dose. Carbon tetrachloride is only one-eighth the cost of thymol. A saline purge is necessary, given about two hours after the drug; an enema may be necessary. Carbon tetrachloride can be given to pregnant women, in whom oil of chenopodium is contraindicated. The minimal dose is 3 min. (0.2 c.c.), and it should be increased by that amount for each year of age, but, as in the case of ascariasis, the efficiency of the drug is probably increased by combining with it 1 c.c. of oil of chenopodium.

The toxic effects which may ensue are due to the effect of the drug on the hepatic cells—a form of delayed chloroform poisoning. Nausea and bilious vomiting may ensue. In instances where any anxiety is aroused, the administration of glucose, 1 dr. frequently, by the mouth, or in 5-per-cent. intravenous injections, is indicated.

It has been stated that the efficacy of carbon tetrachloride is

¹ Toxic symptoms which, as reported, have followed upon carbon tetrachloride treatment, have been shown to be due to carbon bisulphide and phosgene which may be present in some preparations as an impurity.

enhanced by simultaneous administration of the saline aperient, but in the Editor's experience this course is liable to provoke vomiting.

Tetrachlorethylene (C_2Cl_4), which has a pleasanter taste and odour, is said to be equally potent and safe.

Beta-naphthol, given in the same way as thymol, in doses of 15 gr., repeated at intervals of two hours for two or three times, and followed by a dose of salts, is nearly as efficacious, is cheaper and much less unpleasant, and is preferred by some to thymol.

Oil of eucalyptus 30 min., chloroform 45 min., and castor oil 10 dr., one-half first thing in the morning, the other half thirty minutes later, is also an efficient vermifuge in ancylostomiasis, much less unpleasant and much less dangerous than any of the foregoing. It can be repeated for several days in succession.

Convalescence.—The dieting of convalescents from serious ancylostome disease must, for a time, be very carefully conducted. A rich, full dietary is to be avoided until the powers of digestion have become re-established; otherwise, enteritis and diarrhoea may prove very troublesome and retard recovery—perhaps prevent it altogether. Iron and arsenic, which may be given intramuscularly, are indicated as blood restorers.

Prophylaxis.—In devising a system of prophylaxis for ancylostomiasis, the fact that it is by means of the fæces of the already infected that the parasite is spread must be kept prominently in view. Fæcal contamination of the soil and water must therefore be prevented. The promiscuous deposition of fæces about huts, villages, and fields must be interdicted. Abundant and easily accessible privy accommodation must be provided in coolie lines, in miners' camps, in native villages, and along the highways of traffic. In the absence of a more elaborate system of conservancy, pits or trenches will suffice. They may be filled up with earth, and fresh ones opened from time to time. The Chinese plan of storing night-soil for months in large, cemented, water-tight pits is a good one. It is known that if the eggs of the ancylostome are kept in pure fæces the embryo is developed and escapes from the eggs in due course; but it is also known that unless the embryo be supplied with a certain amount of air and earth it soon dies. The thing to be avoided, therefore, is the mixing of *fresh* fæces with earth. By the Chinese system the embryos of the ancylostome are killed and, at the same time, a valuable fertilizer is secured for the agriculturist.

It is manifest that in devising privies and sanitary regulations the habits of the people they are intended to benefit must be taken

into account; if native habits and prejudices are ignored, any system, no matter how perfect it may be in theory, will fail in practice.

The water supply should also be carefully guarded from all possible sources of faecal contamination. Drinking-water, unless above suspicion, should be boiled or strained. So far as possible, facilities for removing all earth and mud from the hands and dishes before food is partaken of should also be provided and their use encouraged.

The destruction of, or the proper disposal of excrement is absolutely effective in the prevention of ancylostomiasis. Badly contaminated ground had better be abandoned. If this should be found impracticable, the soil should be turned over with the plough, or roasted with grass fires, or treated in such a manner that any eggs or embryos it may contain are destroyed or buried. The systematic periodical inspection of plantation coolies is to be recommended. At these inspections all subjects of anæmia or dyspepsia should be put aside for more careful examination; if the eggs of ancylostomes are found in their fæces, a judicious dosing with some of the drugs mentioned may avert serious disease in the individual, and also prevent him from becoming a source of danger to his companions.

Until a few years ago, efforts at the prevention of ancylostomiasis were directed towards treating the surface of the soil, but recent work has shown that the ancylostome larvæ spend a considerable part of their life in the deeper layers.

A most important factor underlying an efficient prophylaxis of ancylostomiasis in a community is the life-span of the infective larva during its existence in a free state in the soil. Practical experience gained by the directing authorities of the "hook-worm campaign" suggests that this is much longer than experimental evidence would indicate. According to Cort, Augustine, and Payne, the life of the infective larva under these conditions does not exceed six weeks, and during that time it does not wander outside a 4-in. radius in a lateral direction, but can migrate to the surface from a depth of 36 in. This view, however, is not generally accepted. Baermann has shown that the larvæ may be recovered with ease from soil thought to be infective; the technique consists in placing the suspected soil in a receptacle, together with a quantity of water; the larvæ then rapidly migrate into the fluid, where subsequently they can be easily found and recognized. (See Appendix, p. 878.)

In view of the great danger to health that exists in certain

countries from this and similar parasites, the sanitary authorities in such places ought to circulate among the people, by means of printed leaflets or posters, a few simple directions for the prevention of ancylostomiasis and kindred diseases. Nicoll has recommended common salt as a prophylactic agent of some potency. It has the advantages of being cheap and, as a rule, easily obtainable. It has an injurious effect upon the larvæ, but requires to be brought into very intimate contact; mere sprinkling is futile. Solid salt, however, when sprinkled on fæces, does not penetrate the mass for forty-eight hours.

Clayton Lane estimates that out of 315 million inhabitants of British India, 45 million wage-earners are subjects of ancylostomiasis. Employers of labour in the Darjeeling district estimate that the labourer's earning capacity when freed from this disease is increased by 25-50 per cent.

An energetic and many-sided campaign against the hookworm, already referred to, is being waged in the United States, Asia, and Africa, financed by Mr. Rockefeller. State and county dispensaries for free examination and treatment of applicants have been established. The total number treated in 11 States in 1912 was 238,755; a Commission has been working for a number of years, and has treated 393,556 people at a cost of a little over a dollar per head. The reports issued by the Commission contain most valuable statistics, of which a few may be quoted. In Panama, in 1916, 30,094 persons were examined, and 80.4 per cent. found infected; of these, 98.2 per cent. received first treatment, and 49.9 per cent. were cured. In Antigua, of the total population, 98.8 per cent. were examined, and 29.8 per cent. found to be infected; treatment was meted out to 92 per cent. of the infected people, and 96 per cent. of these were cured. In British Guiana, out of 3,900 infected natives, only 8.6 per cent. remained as foci of infection at the end of the campaign. In Ceylon, of 4,567 tea-plantation coolies, no less than 95.6 per cent. were found infected. It is said in the Transvaal that ancylostomiasis is rife only in the alkaline mines, not in the acid ones.

Darling recommends that, as the agricultural and mining population within the tropics is so universally infected with hookworm, the detection of individual infections by microscopical examination is no longer necessary. The population should therefore be treated *en masse* by an intensive method. The sanitarian should remember that an individual may be infected, yet not "affected" by the disease. Hence, apparently healthy persons may be a danger to the community.

ANCYLOSTOME DERMATITIS

A form of dermatitis affecting the feet of coolies on plantations in Assam, in the West Indies, and probably elsewhere in the tropics, and variously known as ground itch, pani-ghao, water itch, water-pox, water sores, sore feet of coolies, is ascribed to the penetration of the skin by ancylostome larvæ, and precedes by two to four months the generalized symptoms of ancylostomiasis. The disease is of much economic importance to the planter.

The soil in the neighbourhood of coolie lines is extensively contaminated by fæcal matter. During rainy weather the ancylostome eggs in the fæcal material are hatched, and the larvæ escape into the damp earth. The bare feet of the coolies are constantly soiled with this larva-laden earth; and in this way, in many tropical plantations, Looss's experiment is unintentionally carried out on a large scale. Dermatitis, vesiculation, and it may be pustulation, or even extensive ulceration, and probably ancylostomiasis anæmia, ensue. The services of the affected coolie are lost to the planter till the irritation subsides and the anæmia is cured.

Personal cleanliness and the use of some form of foot covering during the wet season, together with the prophylactic procedures for ancylostomiasis already mentioned, are the special preventive measures indicated as against this disease. Coolies working on irrigated land should be provided, if possible, with high, well-fitting boots. As regards treatment, antiseptic foot-baths and some soothing ointment are indicated.

III. CESTODES

The ordinary tapeworms, *Tænia saginata* and *solium*, and their cystic forms, are common enough in the tropics and subtropics, their distribution being regulated by the presence or absence of their proper intermediary hosts—the ox in the one case, the pig in the other, and by the habits of the people as regards cooking and conservancy.

The broad tapeworm (*Dibothriocephalus latus*) is known to occur in Turkestan, in Japan (where the natives are in the habit of eating raw fish), in Madagascar, and among the natives on the shores of Lake Ngami, South Africa.

The very severe degree of anæmia, referred to with almost wearying persistence in text-books, is not seen, in tropical practice at any rate, in association with this parasite. Cases of natural and experimental infection have been seen in whom no gross blood-changes can be found.

The only cestodes of man which, so far as is known, have any claim to be regarded as more or less special to warm climates are *Hymenolepis nana*, *Sparganum mansoni*, and *S. proliferum*.

Treatment.—The patient should be carefully prepared for anthelmintic treatment. Aperients, either castor oil or salts, should be taken to clear out the bowel for two days beforehand, and the diet restricted to light food. *Filix mas*, extract of male fern, much the most reliable drug in cestode infections, in an ethereal extract, should be taken early in the morning of the fourth day. The dose is 1–1½ dr. and is usually repeated; it is best given in capsules containing 1 dr. each, one at intervals of half-an-hour, for three doses; the patient must then remain quiet, and take a dose of salts an hour or more later. Should the head not appear in the next motion, the eucalyptus-chloroform-castor-oil mixture (p. 598), or oil of turpentine 30 min. in emulsion, if given immediately after the final aperient, may bring it away successfully, especially if combined with a soap-and-water enema. Carbon tetrachloride appears rapidly to anæsthetize tapeworms, especially *T. solium*, and may be combined with oil of chenopodium (15 min.) in the following mixture:

Carbon tetrachloride	3 i.
Oil of chenopodium	:	:	:	:	:	℥ xv.
Liquid paraffin	3 i.

Of this, adults should receive the full dose; children up to fourteen, 4 dr.; children up to eight, 3 dr.; under six, 2 dr. The mixture must be made up fresh daily. One-and-a-half hours after the dose the patient should be given a massive saline aperient (sodi sulph. 480 gr.). Some prefer to employ 1–2 dr. of pulv. jalapæ co. The great difficulty in the case of *T. saginata* is the dislodgement and removal of the head; this cannot be done unless preliminary fasting is strictly observed.

Pelletierina tannate, a mixture of alkaloids obtained from pomegranate stem and root-bark (*Punica granatum*), in a dose of 8 gr., which is slightly soluble in water, followed in two hours by an ounce of castor oil, often proves effectual. The crude bark, 3 oz. macerated in 10 oz. of water, is considered a potent anthelmintic by native races.

Alternative treatment.—The following treatment which is said to be exceptionally successful in removing the head of *T. saginata* has recently been described. The patient should fast the day previous to treatment, but black coffee and water may be drunk freely. At 6 p.m. and again at 6 a.m., 15–30 gr. of magnesium sulphate are given. No breakfast is permitted, but after the

bowels have been opened, half-an-ounce of the following emulsion is administered ; oleoresin of aspidium 60 gr. ; powdered acacia 30 gr. ; distilled water to one ounce ; one hour later a second dose of half-an-ounce is given ; after two hours 30 gr. of magnesium sulphate are again given, and two hours later a large soap-and-water enema. The stools passed should be immediately strained and the head sought for. For the success of this treatment it is essential that the oleoresin should be recently prepared.

To prevent, if possible, the growth of the tapeworm when the head has not been expelled, immediate treatment should be instituted with beta-naphthol in tablet form, 15 gr. to be taken first thing in the morning, on an empty stomach, for ten days.

Section VI.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

CHAPTER XXXVI

VEGETABLE POISONS

AN exhaustive account of the various poisonous plants, their uses and antidotes, is beyond the scope of the present work. All that can be done is to indicate those of most importance to the tropical practitioner.

ARROW POISONS

The arrow poisons employed by native races vary. Some owe their toxicity to micro-organisms such as the tetanus bacillus, others are plant poisons, whilst a third group is obtained from the poisonous secretions of coleopterous larvæ and from snake venom.

The arrow poisons of African tribes are derived from poisonous plants of the genera *Acocanthera*, *Strophanthus*, and *Adenium*. Of these, the first-named genus is the most important; it supplies the arrow poisons used by the East, West, and Central African tribes. They are small climbing shrubs with white or red flowers and violet-tinted fruits. A decoction of the wood is evaporated down to a thick tar-like mass—the poison. The active principle is a powerful cardiac depressant causing heart-failure. The *strophanthus* poison, used in the Congo, Lake Nyasa, and Gold Coast regions, is obtained from decoctions of the seeds of that plant; death takes place through cardiac failure. In South-West Africa the natives extract a poison from the sap of *Adenium boehmianum*, of which the active principle is *eckujin*; this also probably exerts a virulent cardiac effect. The pygmies of the Central African forest use a substance obtained from *Erythrophloeum guineense* mixed with strychnine, while the Waigogo of East Africa employ the sap of *Euphorbia candelabrum*. The Hottentots of South Africa were in the habit of extracting an active and irritating principle from the larva of a cockchafer, *Diamphidia locusta*, which causes a considerable amount of œdema and cutaneous inflammation.

In Asia, arrow poisons are still in use in Malaya, Sumatra, and Borneo, and are prepared from various species of *Aconitum*, *Antiaris*, and *Strychnos*. In Malaya, the upas tree, *Antiaris toxicaria*, provides arrow and dart poisons, of which the active principle is *antiarin*, obtained from the inspissated sap of the tree, and acting in many respects like digitalis; it is called “ipoh.”

In Borneo and Malacca, poisons are derived from *Strychnos ovalifolius*,

and are known as *aker lampong*; they contain both strychnine and brucine, and produce acute respiratory failure.

South American arrow-poisons are all obtained from various species of *Strychnos*, of which the active principle is *curare*; they produce acute respiratory paralysis by action on the motor nerve-endings.

The general treatment of a poisoned-arrow wound should be directed towards preventing absorption of the poison, by applying firmly a constricting bandage or ligature above the site of the wound. If, owing to the barbs, the arrow-head cannot readily be removed at the site of entry, the best method consists in thrusting the head through the skin on the opposite side of the limb. After withdrawing it, the wound must be thoroughly washed out with a 5-per-cent. solution of potassium permanganate; cardiac action must be maintained by stimulants. In the strychnine group, morphia should be given as an antidote.

POISONS USED FOR CRIMINAL PURPOSES

Of inorganic poisons, the one most generally used by tropical races is arsenic in some form, cleverly intermingled, as a rule, with flour, or even inserted into the grains of maize or millet, or introduced into sweets as in Egypt; in Malay, powdered croton seeds or datura are used. Native races usually possess a much wider and more intimate knowledge of organic poisons than do civilized peoples.

In Brazil, common native poisons are derived from *Paullinia pinnata*, which contains an alkaloid, *timboin*, and from the fruit of *Thevetia ahonai*, of which the active principle is *thevetosin*; both of these excite vomiting and cause respiratory failure.

In the Dutch East Indies a poison extracted from the roots of *Milletia sericea* is employed, which produces debility, headache, diarrhoea, collapse, and death.

In the Pacific islands the native poison is obtained from the fruit of *Barringtonia speciosa*.

In India a large number of vegetable poisons are in use. In the Madras and Bombay Presidencies an extract is obtained from the roots of *Nerium odorum*, the white oleander, which contains two glucosides having a specific action on the heart. Similar substances, *urechitin* and *urechitoxin*, derived from *Urechites suberecta*, exert a cumulative action, and therefore sudden death may take place without suspicion of poisoning being aroused.

The juice of an *Asclepias* is used in India as an infanticide; the symptoms induced are vomiting, salivation, and cramps. The roots of various species of aconite (*A. ferox*, etc.) are used for the same purpose; death is said to take place rapidly—in three to six hours, as a rule. Several species of Apocynaceæ, such as *Cerbera odollam* and *Thevetia nerifolia*, the sap and seeds of which contain a glucoside, *thevetin*, are very deadly—death from cardiac failure taking place in from twelve to fifteen hours. In Southern India, Burma, and Ceylon a decoction of the fruit of the *Gloriosa superba*, one of the Liliaceæ, allied to squills, is employed for criminal and suicidal purposes. The active principle, *superbin*, causes gastro-intestinal irritation and cardiac failure within four hours. The commonest poison in India and Ceylon is the datura, one of the deadly nightshades, of which there are several species. The seeds, mixed with food or drink, produce a state of extreme mental exaltation, followed by coma; the active principles are *atropine*, *hyoscyamine*, and *scopolamine*.

In Africa the leaves of *Hyoscyamus fahezlez*, containing *hyoscyamine* and *scopolamine* as active principles, are used by the Tuaregs of the Sahara. On the West Coast a decoction of a cactus, colloquially known as "oro," produces blisters in the mouth, vomiting and gastro-intestinal irritation, collapse, and death within a few hours. In China, opium is the poison most frequently used, especially by women, for suicide.

DISEASES DUE TO THE INGESTION OF POISONOUS FOODS

LATHYRISM

This disease, characterized by various nervous manifestations, such as ataxy, spastic paraplegia, weakness, and muscular pains, without any psychical disturbances, occurs in Abyssinia, Algeria, and India in those districts in which vetches, "Khasari," *Lathyrus sativus* and allied species, form the main article of diet. A similar disease occurs in animals fed upon the same food. The arms and trunk are seldom involved; incontinence of urine and sexual impotence are early and common symptoms. The disease is very chronic and seldom ends fatally. Weeds which contaminate the true khasari, such as "akta" (*Vicia sativa*), contain bases with alkaloidal properties such as *vicine* and *divicine*; the latter in combination with a glucoside produces, on inoculation into guinea-pigs, a fatal disease.

ATRIPLEXICISM

A combination of curious cutaneous and nervous symptoms is known in China under this name. It is an intoxication caused by ingestion of the leaves of *Atriplex littoralis*. The earliest symptoms consist of great itching of the hands, followed by œdema, and often by bullæ as well; the finger-tips may become gangrenous, cutaneous hæmorrhages may occur, and the face and eyelids become cyanotic and œdematous. In many ways the condition resembles Raynaud's disease and erythromelalgia.

ACKEE POISONING (VOMITING SICKNESS OF JAMAICA)

An acute and very fatal condition, locally termed "the vomiting sickness," has been known for many years in Jamaica. It is found principally in rural districts and occurring in what were regarded as circumscribed epidemics. Until recently its causation and nature were neither apprehended nor understood, although several Commissions had attempted their elucidation. To Dr. Harold Scott belongs the merit of clearing up the mystery, and indicating simple and practical methods of prevention, which, if given effect to, must avert a considerable mortality, particularly among children. It is estimated that since 1886 over 5,000 lives have been lost in Jamaica from this cause alone.

The vomiting sickness is confined to the West India Islands, practically to Jamaica, and occurs principally in the cooler months, from November to April.

Symptoms.—A previously healthy child suddenly complains of abdominal discomfort, vomits several times, apparently recovers, and perhaps falls asleep. Three or four hours later, vomiting—now of a cerebral type—recurs. Within a very short time, a few minutes perhaps, convulsions and coma supervene; and death follows, on an average about twelve hours from the oncoming of the initial vomiting, though it may occur in as short a period

as one-and-a-half hours. The case-mortality amounts to 80-90 per cent. In those who recover, convalescence is complete in twenty-four hours.

During the attack the temperature is normal or subnormal, rarely rising to 101°; the pulse is 90 to 100; the respirations are 26 to 30, sometimes, as death approaches, being of the Cheyne-Stokes type. The pupils are slightly dilated and, until near the end, react to light, etc. Unless during the convulsive seizures, there is no muscular rigidity. Post-mortem examination reveals hyperæmia of viscera with a tendency to minute intestinal hæmorrhages, together with marked fatty changes, especially in the liver and kidneys, and sometimes to a less degree in the pancreas and heart-muscle.

Etiology.—Scott has shown, on what must be regarded as convincing



Fig. 152.—Ackee fruit. $\frac{1}{4}$ nat. size. (Photo : Dr. G. M. Vevers.)

evidence—clinical, seasonal, epidemiological, and experimental—that the vomiting sickness is really the result of poisoning by a fruit much used by negroes in Jamaica, called *ackee*, the fruit of *Blighia sapida* (Fig. 152), a tree very common in the island. When mature and in good condition, this fruit is wholesome enough; if gathered before it is quite ripe and before it has opened while on the tree, or if gathered from an injured branch, or opened after falling on the ground, it is poisonous. It would appear that the poisonous element in the immature and unsound fruit is soluble in water, for the "pot water" in which the ackees have been cooked is much more toxic than the cooked fruit; and, further, that the poison is precipitated by alcohol.

Treatment.—An emetic, and washing out the stomach with an alcoholic fluid during the primary vomiting, seem to be indicated. Scott is insistent that the administration of alcohol must be prompt.

Prophylaxis.—When the fruit in various stages falls to the ground, only the opened pods, that is the ripe fruit, should be used for food. The immature unopened pods should all be destroyed.

ALCOHOLISM AND DRUG HABITS

Alcohol poisoning occurs in varying degrees among nearly all native races, and in its symptoms and course does not differ materially from alcoholism in other parts of the world. Rum (65–72 per cent. of alcohol), obtained from the fermentation of molasses, is used in the West Indies and South America; arrack (50–60 per cent. alcohol) is manufactured in India, China, and Java from fermented rice or from palm sap; while a slightly fermented drink known as toddy is obtained from sweet sap of various palms, and is drunk in India, Ceylon, and West Africa. In South America a potent alcoholic drink is made of the fermented juice of *Agave americana*, and is known as “pulque.”

Opium poisoning.—The opium habit, either as eating or as smoking—the symptoms of which are too well known to require description—is common throughout the tropics. Opium poisoning is also a favourite form of suicide, especially among women.

Cannabis indica.—Indian hemp, or *hascheesch*, grows in India, Persia, and Arabia, and is a variety of the common hemp, *Cannabis sativa*. The leaves are powdered down, and either chewed or smoked as a preparation known as *bhang*; an extract of the flowers is known as *ganga*. Both these preparations cause great nervous excitement and, if persistently used, often lead to permanent insanity, the main features of which are hallucinations and illusions. *Hascheesch* in its various preparations, often with the addition of extracts of various Solanaceæ, such as *datura* and *nux vomica*, is habitually taken daily by millions of the inhabitants of Africa and Asia. The most stringent Government regulations have been framed with a view to suppressing trade in this drug.

Kawa or yangona, the powdered root of one of the Piperaceæ, prepared so as to form a beverage, is drunk on festive occasions throughout Polynesia. Formerly the root was masticated by specially selected girls previous to the final steps in the preparation of the drink; this practice was a prolific source of tuberculosis, and was on that account prohibited. Over-indulgence in kawa induces a state of hyperexcitement, with loss of power in the legs. Chronic intoxication induces a condition of debility, with coarse roughened skin.

Betel.—The chewing of betel, the leaves of *Piper betel*, together with lime and areca nut (*Areca catechu*), is a common practice in India and Ceylon, and generally throughout the East. The mouth, lips, and teeth are stained a bright-red colour. It produces a flushing of the face, has a mild stimulant and possibly anthelmintic properties. In Central Africa the nuts of the kola tree (*Sterculia sp.*) are chewed habitually, and act, like betel, as a muscular stimulant, without, it is said, producing any detrimental effects.

CHAPTER XXXVII

ANIMAL POISONS

SNAKE POISON AND SNAKE-BITE, POISONOUS FISHES, SPIDERS, AND CENTIPEDES

POISONOUS SNAKES

THE anatomy and classification of snakes are dealt with in the Appendix (p. 844); the best-known and most dangerous species are there described.

The specific action of the venoms appears to depend upon the ferments and lysins they contain. As far as is known, the following substances enter into their composition, viz. fibrin ferments, proteolytic ferments, cytolytins acting upon red cells, leucocytes, epithelial and nerve-cells; agglutinins, and neurotoxins, with affinity for all nervous tissue, and especially for the respiratory and vasomotor centres. The neurotoxins preponderate in the venom of the colubrines, while those which act upon the blood and cardio-vascular system are most characteristic of the viperines; in the Australian colubrines both classes of toxins may be found.

Symptoms of snake-bite in man.—The physiological action and symptoms produced by snake venoms can be classified into two groups, the colubrine and the viperine.

1. *Colubrine*.—In the case of cobra-bite (Fig. 153) there is severe pain in the part, which soon becomes inflamed and cedematous. After an interval of an hour the patient becomes dull, apathetic, and unable to stand. Nausea and vomiting, with profuse salivation and paralysis of the tongue and larynx, supervene. Soon the respiratory centre becomes involved, and respiration ceases. Should the patient survive the paralytic symptoms, recovery is rapid. The pupil is contracted throughout.

The bite of the krait (*Bungarus fasciatus*, Fig. 154) is extremely dangerous, especially in northern India; the symptoms are similar to those produced by the cobra.

The symptoms caused by the bite of the Australian colubrines may not be very severe, but the constitutional effects appear with great rapidity—sometimes in as short a period as fifteen minutes.

A feeling of faintness and an irresistible desire to sleep are soon followed by paresis of both legs, vomiting, and cardiac paralysis. The pupil is widely dilated and insensible to light. Should the patient survive the coma, recovery is complete and no sequelæ occur.

2. *Viperine*.—As the type of lesion produced by the viperines, that of Russell's viper (*Vipera russelli*, Fig. 155) may be described.

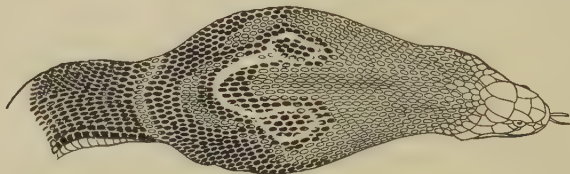


Fig. 153.—The cobra (*Naja tripudians*).



Fig. 154.—The krait (*Bungarus fasciatus*).

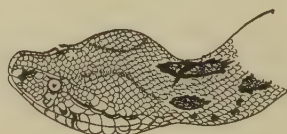


Fig. 155.—The daboia (*Vipera russelli*).

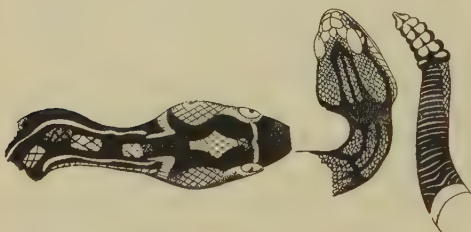


Fig. 156.—The phoorsa (*Echis carinatus*).



Fig. 157.—Rattlesnake (*Crotalus terrificus*).

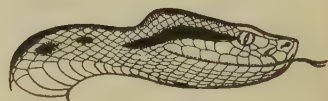


Fig. 158.—*Trimeresurus lanceolatus*.

This species is extremely deadly; the bite causes severe pain with rapidly forming and extensive œdema, together with blood-stained discharge, and ecchymoses around the site of the punctures. Collapse, small thready pulse, nausea and vomiting, dilated pupils insensitive to light, soon supervene, together with a loss of consciousness more or less complete, from which a temporary recovery sometimes occurs. Should the effects of the now diffused toxin wear off, the local condition of the wound becomes aggravated;

extensive local suppuration and sloughing, malignant œdema, or even tetanus and hæmorrhages from the mucous surfaces—hæmaturia or melæna—may occur. There is no paralysis of the muscles, but Rogers has shown that the viperine toxin produces a vasomotor paralysis. It is more easily destroyed by caustic agents than colubrine venom.

The bite of *Echis carinatus* (Fig. 156) is less dangerous than that of the daboia, but is in many ways similar in its effects.

The bites of the rattlesnakes—*Crotalus* and *Trimeresurus* (Figs. 157, 158)—are remarkable for the local disturbance they produce. Constitutional paralytic symptoms come on quickly, usually in less than fifteen minutes. Should the patient recover from this state, the swelling and discoloration extend up the limb and trunk, and general symptoms of blood-poisoning with pyrexia, restlessness, and delirium set in. The wound itself suppurates freely and may become hæmorrhagic, or even gangrenous. The symptoms produced by the bite of the European vipers resemble those of *crotalus*, but are much milder.

The mortality from snake-bite, even of the most venomous varieties, is not so great as is popularly supposed; it is estimated at about 30 per cent. That it should not be more is probably due to the fact that, unlike what takes place in experimental animals, the reptile is seldom able to inject a full dose of venom. If given a fair chance, the cobra is able to inject no less than the equivalent of twenty lethal doses at a time.

Treatment.—To be effective, all treatment should be vigorously and promptly applied. It should be directed, firstly, to prevent absorption of the poison; secondly, to neutralize, as far as possible, its toxic effects. A ligature should be tied around the limb, immediately above the bite; for this purpose, if it is at hand, a stout indiarubber band, firmly applied, is the best ligature. In the case of the colubrines, this probably has little or no effect in preventing the absorption of the neurotoxins, but in the case of the viperines it is no doubt very effective in so far that it localizes the fibrin ferments, causes extensive intravascular clotting in the bitten part, prevents the process from becoming generalized, and affords time for the action of remedies.

Amputation of the part above the bite has been proved to be effective if performed *immediately*.

The next steps must be directed towards destroying the poisons remaining at the site of injection. This is best effected by freely incising the bite in the direction of the lymphatic and venous circulation. The wound should then be well swabbed out with a

strong solution of potassium permanganate; this destroys any toxin with which it comes in contact. Some advocate the rubbing-in of crystals of the same substance. Acton and Knowles have lately advocated the injection of 10–20 c.c. of a 5-per-cent. solution of gold chloride in ox-bile as being an improvement upon potassium permanganate, and recently have stated that dichloride of platinum (1:2,000) is even better.

Contrary to the popular idea, sucking the wound is useless.

Alcohol and strychnine were formerly regarded by some as antidotes, but are now known to have no efficacy whatsoever.

Serum treatment.—It has long been known that immunity could be produced in animals by repeated and progressive inoculation of venom; a similar result is produced in men who have been repeatedly bitten by snakes of one species. This immunity, however, is specific only for the venom of the particular species. Calmette attempted to produce, in *antivenene*, a serum which should be active against all snake venoms, but his claim to have done so has not been substantiated.

The serum prepared against cobra venom is found to be antitoxic to the homologous venom, and to a certain extent to that of *Bungarus fasciatus*, but is without action on the viperine venoms daboia, echis, trimesurus, and crotalus. The serum produced against daboia venom has no action whatever upon the venoms of naja, bungarus, etc.

In practice one is met with the very important drawback to the use of an antiserum that, though specific towards some other species of snakes, it may be impotent as regards the particular species concerned. The only practical method of meeting this unfortunate circumstance is to issue an antiserum effective against the most common and the most dangerous snakes in any given country. All antivenenes are relatively weak in their action as compared to antidiphtheritic and antitetanic serums. The antivenene should be injected in large amounts and as soon after the bite as possible. Acton and Knowles have demonstrated that such a serum must be given before the minimum lethal dose of venom has been absorbed, and that it requires no less than ten minutes to find its way into the circulation. The injection should be done *intravenously*, and at least 100 c.c. should be given. In India the serum treatment, if available, should be employed in every case, on the chance that the snake was either a cobra or a daboia.

There is still much work to be done before an efficient polyvalent serum can be produced. One of the difficulties encountered is that every injection of venom into the horse for the production

of immunity gives rise to abscess-formation, and that the whole process of preparation lasts from a year to a year and a half.

Other measures.—Little else can be done, except to keep the patient warm. Small doses of alcohol, ammonia, and strychnine should be given as stimulants, but the practice of exhibiting almost poisonous doses of alcohol cannot be too strongly deprecated. Rogers has advocated, on physiological grounds, the employment of adrenalin in those snake-bites in which the toxins have a marked paralytic action upon the vaso-motor centres. Acton and Knowles have advocated artificial respiration in colubrine poisoning.

VENOMOUS LIZARDS

All lizards are absolutely non-poisonous, with the exception of a single genus, easily recognized, inhabiting Mexico and Arizona. This genus, *Heloderma*, consists of two species, *suspectum* and *horridum*. both heavy, stout lizards yellow or shrimp-pink in colour, with black bead-like scales. They are desert-dwellers, and store fat in their swollen tails to tide them over periods of famine. They are popularly known as the "Gila monsters,"¹ because they were first discovered near the village of Gila.

The poison apparatus is in the lower jaw, where venom-secreting sub-maxillary glands are connected by ducts with grooved teeth. The symptoms of poisoning start with paralysis. A large dose produces dyspnœa and convulsions. Post-mortems on animals show a greatly dilated heart and venous congestion in the internal organs. Changes in the spinal-cord ganglion cells have also been observed.

POISONOUS FISHES

Poisonous fishes exist in most tropical waters, especially among the coral reefs of the Pacific and Indian Oceans. Their venom may be conveyed to man either through their bite or by means of stings. In the one case the poison is secreted by certain epithelial glands within the mouth; in the other, by poison-glands connected with barbs in the dorsal fin. The former class comprises more than one hundred species of the

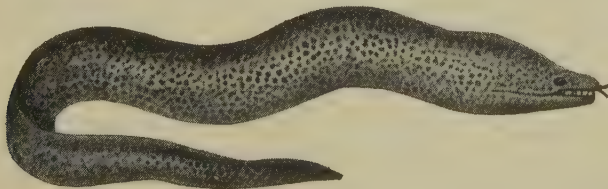


Fig. 159.—*Muræna moronga*. (After Calmette.)

genus *Muræna*, all of which possess powerful teeth capable of inflicting bites. (Fig. 159.) The poison secreted by the glands courses down the hollow teeth. The effect of the venom on man is neuro-cardiac. The other class contains a great number of widely separated genera. In some, the poison

¹ Pronounced Heela.

finds its way to the exterior only when the barbs are broken, and produces severe inflammation in the wound and, it may be, tetanic symptoms. *Synanceia*, a spinous species, is widely distributed throughout the Indian and Pacific Oceans; *Plotosus anguillaris*, known as "machoirá" in Mauritius, has a similarly wide distribution; while *Saccobranchus fossilis*, in the waters of India and Ceylon, produces similar symptoms.

In South American waters, several species of *Thalassophryne* have similar dorsal spines containing a central poison-duct connecting with the glands. Species of *Trachinus* found in northern waters, as well as in the Mediterranean, have two sets of poison barbs, on the operculum as well as on the dorsal fin. The venom has a general action on the heart, besides the purely local effect.

Many species of *Scorpena*, over forty in all, are found in tropical waters; their integument is provided with numerous rays, the stings of which may excite convulsions and even cause death.

POISONING FROM THE INGESTION OF POISONOUS FISHES

Cases of fish-poisoning arising from the eating of flesh of fishes containing some intrinsic toxin occur more commonly in the tropics than in more civilized countries. In many instances these fish may be eaten with safety except at certain seasons of the year; in others the poisonous qualities are acquired only after feeding or living in certain localities.

The barracouta (*Sphyræna barracuda*) is eaten widely throughout the South Atlantic; it is the large fishes, especially those that are spawning, which are apt to be poisonous, and the symptoms are mainly gastro-intestinal.

There are various sprats (*Clupidae*) in tropical waters which are apt to acquire poisonous properties; among them is *C. longiceps*, a sardine found in Ceylon waters, which occasionally may produce collapse and even death.

Many species of the widespread genus *Tetodon* are poisonous, such as the "death-fish" of Hawaii—*T. hispidus*—while other species occur in Japanese and Korean waters. The poison is contained in the ovaries and in the eggs, and causes gastro-intestinal and nervous symptoms, sometimes culminating in syncope or coma.

The flesh of certain large fishes normally constituting excellent food, such as the king-fish (*Scomberomorus cavalla*), may occasionally exhibit toxic properties.

In all forms of fish-poisoning the most effective treatment is to evacuate the poison by washing out the stomach and administering purgatives. Other symptoms must be treated on general lines with stimulants, hot-water bottles, etc. and injections of morphia, if necessary, to alleviate the pain.

SCORPIONS AND SPIDERS (ARACHNIDA)

Scorpions are very common in the tropics, and their stings are very painful and cause a considerable amount of inconvenience, though they are not exactly dangerous, except to young children, in whom, in addition to local symptoms, muscular cramps, profuse perspiration, pyrexia, vomiting, and convulsions may be produced. Deaths have been reported from North and South Africa, the West Indies, Mexico, Korea, and Manchuria.

In southern Europe and North Africa the black scorpions, *Euscorpius italicus* and *Buthus maurus*, in Mexico a species known as the "durango" (*Centruroides*), in Manchuria *Buthus martensi*, are specially dreaded. (Fig. 160.)

The paired poison-glands are situated in the last or postanal segment of the tail, which is jointed and very flexible, so that it can be curved forwards

over the body when the scorpion is striking. The venom which it ejects is in many respects like that of the cobra, but far less toxic.

In the *treatment* of scorpion-sting in children, it may be necessary to incise and thoroughly wash out the sting with a strong solution of potassium permanganate. In adults, pain is the predominating symptom, and this, according to Tomb, can be immediately relieved by a drop of liquor ammoniæ fortis, which can be applied with the stopper of a bottle. A more liberal application of diluted ammonia is also effective, but not so immediate in action. Dyce Sharp, from experiences mostly in his own person, warmly advocates immediate injection of an ampoule of novocain and adrenalin in the vicinity of the sting. For the severe intoxications of children, Todd has produced an efficient antitoxin. The venom extracted from the dried stings and venom-glands by means of normal saline is toxic to the horse, goat, and most laboratory animals; while the desert fauna, such as the desert rat, the jerboa, the fennec fox, and the hedgehog are immune. The antitoxin has

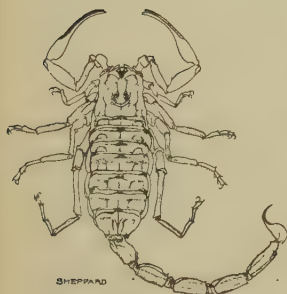


Fig. 160.—Scorpion
(*Buthus* sp.). Half nat.
size.



Fig. 161.—*Latrodectus*
firsti. $\times 2$. (After
Hirst, "Journ. Economic
Biol.")

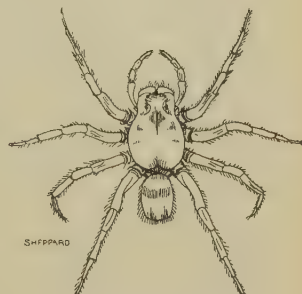


Fig. 162.—*Lycosa tarantula*.
Half nat. size.

been prepared from horses by subcutaneous injection of graduated doses of venom. In doses of 5 c.c. it exerts both a prophylactic and a curative action.

Spiders.—Nearly all spiders (*Araneæ*) possess poison-glands, the venom of which is injurious to insects, but only a few species are dangerous to man. Certain species of the genus *Latrodectus* are believed to be very poisonous. In New Zealand one species, *L. hasselti*, known as the "katipo," in southern Europe *L. tredecimguttatus*, the "malmignatte" (Fig. 161), and in North and South America *L. mactans*, *L. curacaviensis*, and *L. geometricus* occur.

The toxin of the poison-glands has been shown to be a powerful hæmolysin, causing inflammation and œdema at the site of injection, together with numbness of the part and, it may be, an urticarial rash. Sloughing of the skin in the neighbourhood of the bite may occur. *Treatment* consists in washing out the wound with a solution of potassium permanganate (1 : 4,000), and administering the drug in doses of one teaspoonful every two hours.

In Peru a pruning spider, *Glyptocranium gasteracanthoides*, which lives in the leaves of vines, and is identified by its ash-grey colour and large globular

abdomen with two prominent tubercles, produces, according to Escomé, the same symptoms as *Latrodectus*, and sometimes hæmaturia.

The true "tarantula" spider, *Lycosa tarentula* (Fig. 162), occurs in Southern Europe. Mysterious properties have been attributed to its bite; apparently in some specially susceptible people œdema of the eyelids and pyrexia are apt to result. The so-called tarantulas of tropical countries are bird-eating spiders belonging to the family Mygale. They are trap-door spiders, terrestrial in their habits, with prominent projecting mandibles which give them a terrifying appearance. The North African species, *Chætopelma olivacea*, is much feared by the Arabs; its bite is said to give rise to acute inflammation.

CENTIPEDES (MYRIAPODA)

The Chilopoda, to which the poisonous genus *Scolopendra* belongs, are widely distributed in the tropics. They are large species, and possess a poison apparatus at the base of the first pair of appendages, which are modified so as to form jaws. The tropical species, *Scolopendra morsitans*, reaches a large size, up to 6 in.; the venom causes both local and general symptoms. The site of the bite becomes inflamed and the starting-point of a lymphangitis; dizziness, headache, and vomiting may ensue. *Treatment* consists in bathing the part with a strong solution of ammonia, 1 : 5 or 1 : 10. It may be necessary to give hypodermic injection of morphia to allay the pain.

CHAPTER XXXVIII

MYIASIS AND LEECH INFECTION

UNDER the term "myiasis" it is customary to include a number of traumatic conditions of the tissues caused by partial parasitism by the larvæ of certain *muscoïd* flies.

Some of these flies deposit their eggs or larvæ in wounds or in the natural openings of the body; in other cases the grubs, on hatching, burrow into the subcutaneous tissues; others imitate the habits of a tick, and emerge from their hiding-places to feed on the blood of man by puncturing the skin. Intestinal myiasis appears to be an accidental condition in which the larvæ pass through the intestinal canal.

NASAL, AURAL, AND OCULAR MYIASIS

The screw-worm fly, *Cochliomyia* (*Chrysomyia*) *macellaria* (Appendix, p. 830), is a common insect in America, ranging from Canada to Patagonia. It is most active during the heat of the day, and normally deposits its eggs upon open wounds or on dead animals. It attacks people sleeping in the open air, especially those who have offensive discharges which attract it.

Comparatively frequently the fly lays its eggs in the nasal and aural cavities, as well as on open sores. The larvæ, known as screw-worms, burrow into the tissues, devouring in their passage mucous membrane, muscle, cartilage, periosteum, and even bone. They may penetrate the brain and cause death. (Fig. 163.)

Chrysomyia bezziana (Appendix, p. 830) is a true myiasis-producing fly; it never breeds in dead, but always in living tissues. It has a wide distribution, being found in India and Cochin China. It appears to have a predilection for human beings in India, the female, as in *Cochliomyia macellaria*, laying her numerous eggs in the nasal cavity or in tissues from which an offensive discharge emanates.

Rhinæstrus purpureus (Appendix, p. 834).—The larvæ of this species are parasitic in the nasal passages of equines in southern Europe, Asia Minor, and Africa, but occasionally the fly attacks man, depositing its eggs in or near the eye, where the larvæ may be seen, shortly after hatching, moving beneath the conjunctiva, and may lead to the loss of this organ.

Wohlfahrtia magnifica (Appendix, p. 827) belongs to the family Sarcophagidæ, or flesh flies; it is the only specific myiasis-producing fly found in man in Europe; it has a wide distribution in Asia Minor and Egypt. In habits it is similar to the species previously described.

SUBCUTANEOUS MYIASIS

In South America the "macaw-worm," or "Ver macaque" (p. 833) (*Dermatobia cyaniventris*), infects cattle and indigenous mammals, and also man.

The eggs are deposited on the skin or clothes of human beings, and do not hatch for a day or two. When hatched, the larvæ penetrate the skin and produce an inflammatory tumour, from the aperture of which there exudes a seropurulent fluid containing their black fæces. They have been reported from various regions of the body, and their presence is usually accompanied by great pain, especially when they are actively moving. Busck reports that before they reach maturity the larval skin may be shed and exude from the opening in the skin of the host. In removing them there is



Fig. 163.—Native with *Cochliomyia macellaria* in nostrils and frontal sinuses : early stage. (Photo: Dr. C. W. Daniels.)

apparently no need to use a knife, for the aperture of exit may be widened by stretching with forceps, and the larva then slips out, aided by properly applied pressure, for its narrow end is situated towards the opening in the skin.

In tropical Africa the Tumbu fly, or Ver du Cayer (*Cordylobia anthropophaga*, p. 831), produces much the same results. According to Roubaud, Blacklock, and Thompson, the eggs are first deposited on the ground, and the active young maggot attacks and penetrates the skin of its host, especially on the forearm, scrotum, upper part of the thigh, and buttock. The lesion resembles an inflamed tumour, from which the larva emerges in six or seven days. In the ordinary course of events these tumours do not suppurate. The fly usually attacks other mammals besides man.

LARVA MIGRANS

Synonyms.—Myiasis Linearis ; Creeping Eruption ; Dermatitis Linearis Migrans.

This condition (Fig. 164), first described by Lee in 1874, and at a later period by Crocker, is said to be common in Russia and, according to Kirby-Smith, extremely frequent in Florida. Certainly it is not infrequent in the tropics, especially in Ceylon and South Africa. Here multiple lesions on the legs and feet are produced by the burrowing under the skin of a larval nematode—*Agamonomatodum migrans* (Ransom), of the family *Strongyloidæ*. The larva is very minute, being $\frac{1}{50}$ in. in length and $\frac{1}{125}$ in. in breadth. It burrows under the epidermis where it can be found in microscopic sections of the skin.

In Florida the disease has a definite seasonal prevalence during the summer



Fig. 164.—Larva migrans. Infected at Durban, April 20, 1921 ; first symptoms noted July 22, 1921. (*Orig. case.*)

months, following periods of rainy weather. Most of the cases originate on the beach above high water mark. There is some evidence that it is connected with sewage disposal. Rats may be the host of the adult worm.

It is possible, as Fülleborn and da Rocha-Lima suggest, that the tropical form differs from that described in Russia and America. The former appears to be due to the burrowing of a fly larva under the epidermis. These larvæ have been identified as being *Hypoderma*, *Gastrophilus hæmorrhoidalis*, and *G. veterinus*.

The manner in which the larva enters the skin is unknown. Children are mostly attacked between the fingers and toes.

Unlike the itch-mite, it burrows on indefinitely, like a mole, and forms a red line or narrow raised ridge $\frac{1}{8}$ in. broad. The parasite appears to travel at the rate of $\frac{1}{2}$ –1 in. in twenty-four hours. The line zigzags and twists about, but does not bifurcate, and may be found in any part of the body—the face,

chest, or more particularly the soles of the feet and the legs. While the advancing end of the line progresses, the opposite end fades away. The only subjective symptom is itching. The disease may be of very long duration, and is accompanied by intense itching; sometimes bullæ are formed.

Austmann has used Lombard's method of clearing the living skin to demonstrate the larvæ of *Gastrophilus* in cases produced by this insect. Ordinary machine-oil is used and the epidermis cleared around the line of creep. Using the binocular dissecting microscope the parasite may be seen lying between the cornified and granular layers of the epidermis. With a magnification of 150 diameters, details of structure can be clearly seen.

Treatment by injection of cocaine and parasitocidal substances in advance of the migrating larva has so far proved to be unsatisfactory. Excision of the portion of the burrow containing the advancing larva should be attempted. Ethyl acetate, applied on cotton or gauze or used in a flexile collodion, is effective in many cases. Refrigeration with ethyl chloride, carbon-dioxide snow, or crushed ice with salt, has been used successfully.

BLOOD-SUCKING LARVÆ

Auchmeromyia luteola (Appendix, p. 828), the larva of which is commonly known throughout the Congo as the "floor maggot," has a wide distribution throughout tropical Africa, from Northern Nigeria to Natal. The adult fly is usually found among the thatch and beams of the walls and roofs of native huts, and deposits its eggs in crevices of the mud floors. Here the larvæ hatch and move about in the moist earth. They emerge from their hiding-places and feed mainly at night.

The sucking of blood is effected in a curious manner: the head segment is retracted, and the lips of the second form a sucking disc attaching the larva to the skin of the host; the skin is scarified by the curved hooks, and thus blood is drawn. The larva itself soon assumes a red colour due to the absorbed blood. It is said that the bite is not irritating.

The larvæ of *Cordylobia anthropophaga* (see p. 831) and *Dermatobia cyani-ventris* (see p. 833) burrow under the skin and form subcutaneous abscesses. In the case of the former a remarkable example of metazoan immunity has been found to be produced by Blacklock and Gordon (see p. 832).

INTESTINAL MYIASIS

A residence in the alimentary canal of some vertebrate animal is a regular feature in the life-history of many dipterous insects. The eggs of the insect are either licked from the skin or swallowed in the food on which they had been deposited. In this way they are transferred to the stomach, where, after a time, the larvæ are hatched out and undergo development. In due course they appear in the faeces. Man is not infrequently victimized in this way, especially in tropical countries. Sometimes, until a correct diagnosis is arrived at, not a little alarm is caused by the appearance of these creatures in the stools or vomit. They are easily recognized. The ringed, cylindrical body, $\frac{1}{2}$ -1 in. in length according to species, broad at one end, tapering at the other, and usually beset with little spines or hairs, is sufficiently diagnostic. (Fig. 165.)

Already we know over twenty species of diptera whose larvæ have been found in or expelled from the human intestinal canal.

In Europe the majority of cases of intestinal myiasis, a not infrequent occurrence, are caused by *Fannia canicularis* (a fly closely resembling the

common housefly, and erroneously considered a young form of the latter on account of its smaller size) and the closely related *F. scalaris*. Occasionally pains in the abdomen, vomiting, and diarrhœa may ensue, and there may be evidences of toxic absorption; more usually these occur where the ingested larvæ are those of the cheese maggot, *Piophilæ casei*. Larvæ of the common housefly (*Musca domestica*) have been found in numbers in the stomach in the Philippines.



Fig. 165.—Larva of *Calliphora vomitoria*.

A dose of castor oil will probably suffice to expel any of these creatures that may not have been passed spontaneously.

A rational prophylaxis would consist in the covering up of food after it has been cooked, in order to prevent the access of flies.

Instances in which the larvæ have been discharged per urethram have also been met with, though more rarely.

LEECH INFECTION

In the grass and jungle lands of many tropical and subtropical countries land-leeches, probably of special species, often occur in great abundance; so much so that in some circumstances they may prove to be something more than a nuisance. The *Hæmadipsa zeylanica* is one of the most active, as well as best known, of these. Before feeding, when outstretched, it is about an inch in length and about the thickness of a knitting-needle. It clings to a leaf or twig, awaiting the passing of some animal, on to which it springs with remarkable activity. It at once attaches itself to the skin and

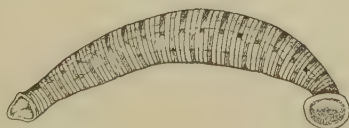


Fig. 166.—*Limnatis nilotica*.—Half nat. size. (Sheppard, del.)

proceeds to make a meal on the blood. Animals are sometimes killed in this way; men even have been known to succumb to repeated small bleedings by these pests. It is necessary, therefore, when passing through jungle lands in which leeches abound, to have the feet and legs carefully protected. The bite is not infrequently the starting-point of a troublesome sore.

In the south of Europe and in the North of Africa the horse-leech, *Limnatis nilotica* (Fig. 166), sometimes gets into the gullet and nostrils of men as well as of animals. It has occasionally caused death by entering and occluding the air-passages. These leeches are a source of inconvenience to French troops in Algeria, and are mentioned as occurring in Napoleon's army in its retreat

through the Sinai Peninsula; and several cases were noted among British troops during the late Egyptian and Palestine campaigns. In Formosa, Manson heard of and saw several instances of a similar form of parasitism both in men and in monkeys. To what particular species the leech in these cases belonged is not known. Doubtless, when very young the leeches were taken in unperceived with foul drinking-water, and, wandering round the soft palate, found their way into the nose. Occasionally, in the cases referred to, the animals would protrude from the nares and wander over the upper lip. For a long time they contrived to elude all attempts at capture. By dipping the face in cold water they could generally be persuaded to show themselves. In one instance the leech dropped out spontaneously. In another—an American naturalist who had been travelling much in the interior of Formosa, and who had suffered from severe headache and profound anæmia, the results of repeated epistaxis—Manson succeeded in removing the leech by attaching through a speculum a spring forceps to its hinder end, and afterwards injecting salt and water. It would be well to bear in mind that in tropical countries persistent headache, associated with recurring epistaxis, may be caused by a leech in the nostril.

Section VII.—TROPICAL SKIN DISEASES

CHAPTER XXXIX

NON-SPECIFIC, BACTERIAL, AND FUNGOUS DISEASES, ETC.

I. NON-SPECIFIC SKIN DISEASES

LEUCODERMA (Fig. 167)

LEUCODERMA or vitiligo is extremely common throughout the tropics, and is by no means confined to any particular race. Almost any part of the body may be affected. The atrophied, unpigmented patches of skin slowly enlarge in a peripheral direction, and may coalesce. Occasionally the whole body is affected, and a certain amount of symmetry may be observed; the hair of the affected parts may also become white. The texture and glands of the skin remain normal. The etiology of the disease is unknown, but it is thought to be a tropho-neurosis. No treatment is of any avail. It is possible that those cases with a positive Wassermann reaction are syphilitic in origin and may be benefited by antisymphilitic treatment. Care must be taken not to mistake this condition for the depigmentation which is commonly seen in macular leprosy.

CHELOID

Synonym.—Keloid.

The term cheloid is applied to an overgrowth of fibrous tissue in the cellular layers of the corium. Hypertrophic scars are common enough in Europeans consequent upon surgical scars or burns, but there are those who are predisposed to develop the extensive hyperplasia which is known as cheloid. Central African negroes are especially liable, and in some tribes cheloidal scars on the back, thighs, or chest constitute a readily recognizable tribal mark. Similar fibrosis may occur in these people consequent upon a cautery, or marking the site of a healed syphilitic chancre, or even mosquito-bites.

When fully developed, the growth is well defined; on a white skin it is pinkish or brownish in colour, but has a distinct red or

chocolate tinge on a dark person. Growth takes place very slowly, and rarely sarcomatous changes may supervene in the fibrous tissue. The growth may cause intense pain when forming, or give rise to a continuous ache.

Treatment.—The most efficacious method, according to MacLeod, is by radium. A full-strength radium plate is used, and is screened off by a silver sheet 1 mm. in thickness. The exposure



Fig. 167.—Leucoderma in a Cingalese.

should be one of 18–30 hours. Less brilliant results are obtained by means of CO_2 snow, especially in early lesions. Electrolysis (3 ma.) is also useful, while occasionally X-rays are satisfactory.

II. BACTERIAL SKIN DISEASES

TROPICAL SLOUGHING PHAGEDÆNA

Synonym.—*Ulcus Tropicum*.

Geographical distribution.—Sloughing phagedæna is common in most tropical countries, particularly in those with a hot, damp climate, principally in the jungle. These sores are often named after

the regions in which they are specially prevalent—Mozambique ulcer, Yemen ulcer, etc.

Occasionally this disease assumes epidemic proportions. Thus, Lloyd Patterson described one such epidemic which “swept like a plague up the whole of Assam,” seriously interfering with the efficiency of the labour force on the tea plantations.

This form of phagedænic ulcer was, according to Balfour, very common among the carriers attached to the East African Force during the Great War, and accounted for a considerable amount of invaliding

Etiology.—Prowazek attributes these ulcers to *Treponema schaudinni*.

Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, by bandaging a swab smeared with discharge from a typical sore on to the surface of an abrasion from which the scab had been removed, succeeded in producing a characteristic sore.

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven slave gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are coendemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood calcium-content is said to be much diminished, probably as the result of deficient dietary.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The formation of this may be attended with some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of an inch to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease

and the slough be gradually thrown off. Then it is seen that not only have the skin and superficial fascia been destroyed, but that in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have shared in the gangrenous process. Fortunately, in many instances the deeper structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed; in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix.

Diagnosis has to be made from the ulceration of yaws, syphilis, oriental sore, varicose ulcers, and veld sore.

Treatment.—As recent observations in Kenya colony and Tanganyika Territory have shown that dietetics play a very important part in the production of *ulcus tropicum*, it is of the first importance to endeavour to correct any cachectic state which may be present. Thus good food, fresh vegetables, lime-juice, and quinine are almost invariably indicated. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedænic process, is usually of great service. Locally, an endeavour must be made effectually to destroy the germ by the application of some powerful and penetrating caustic to the diseased surface. With this view, on the strength of considerable experience, Manson recommended that the patient be put under chloroform and the slough thoroughly dissolved off by the free application of pure carbolic acid, a piece of lint on a stout stick being used as a mop for the purpose. Thereafter the limb should be elevated, and placed under some improvised irrigator from which a weak, warm, antiseptic solution should continuously trickle over the now clean surface. If the phagedænic action recur, the carbolic acid must be promptly reapplied as often as may be necessary. On healthy granulations springing up, the ulcer is to be treated on ordinary principles.

The most recent and most successful treatment appears to be with formalin. The strong commercial solution is applied lightly once a day for two or three days, followed by a bismuth-paste dressing directly a scab has formed. It may be necessary to repeat the treatment. The healthy tissues surrounding the sore should be supported by Unna's plaster. Whenever available, X-rays should be tried. Sometimes recourse has to be had to amputation. Insufflation of pure acid potassium tartro-bismuthate causes a rapid diminution of the pain. Of this salt, 1 grm. should be applied daily; an average case requiring four to five dressings.

Patients with this disease should be regarded as infective and, so far as possible, be isolated.

VELD SORE

Synonyms.—Septic Sore ; Desert Sore ; Barcoo Rot.

Geographical distribution.—This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaigns, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine, and Mesopotamia during the Great War. In South Africa it is familiar to sportsmen and travellers.

Etiology.—The cause of this condition has long been obscure. In 1916 Craig, working in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the etiology of all veld sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a pure culture of the Klebs-Löffler bacillus may be obtained on Löffler's serum. This organism is pathogenic to guinea-pigs and quails, and its lethal effects may be neutralized by injection of antidiphtheritic serum. In the serous contents of the blebs the typical granular bacillus may be observed in stained preparations.

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with camels. The rate of incidence coincided with that of a widespread epidemic of faucial diphtheria.

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the forearm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise *de novo*, or be superimposed on some abrasion.

A regular sequel of events precedes the actual ulceration. At first a *vesicle* full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair-follicle ; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting, it leaves behind a shallow *ulcer* covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Fig. 168.)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a *chronic stage*. At this stage they are characteristic in appearance, and perhaps are more familiar to tropical practitioners and medical officers than when in the incipient stages. The ulcers are punched-out, circular in outline, with undermined edges and thickened margins; their base is covered with



Fig. 168.—Veld sore.

Mesopotamian case of two-and-a-half years' duration. Healed in ten days with 4,000 units of anti-diphtheritic serum.

grey-coloured and scaly debris, beneath which one can frequently distinguish an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and the thickened tissue has a cyanotic appearance. In sores in which healing does take place a thin paper-like scar remains, and

persists for several years. The actual ulceration may continue for two years or longer.

The Klebs-Löffler bacillus can only be isolated with ease from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration.

Typical diphtheritic pareses or paralyzes have been observed in association with these sores. In one series this complication occurred in 27 per cent. of cases. Paralysis of the palate, arms and legs, and accommodation paralysis of the iris, have been observed. There may be ataxia, loss of knee-jerks, anæsthesia, and inco-ordination, recalling at first sight locomotor ataxia or beriberi; indeed, these diseases have been diagnosed in cases of this peripheral neuritis. Walshe has pointed out that the initial local paresis is in anatomical relation to the site of the infective focus.

Treatment.—The specific treatment for this kind of ulceration is antidiphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 4,000 units should be given, and should be injected subcutaneously in the vicinity of the sores. The sores themselves may be dressed with lint soaked in the same serum or with weak formalin.

Prophylaxis.—Protecting exposed parts of the body, especially the knees, against abrasion, in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this substance as far as possible.

BOILS

The anatomical and clinical features of this painful affection are too familiar to require detailed description. Suffice it to say that a boil is produced by the proliferation of *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, or other pyogenic micro-organisms, in the skin and subcutaneous tissue; that the organism gives rise to local and limited infiltration of the tissues with lymph, leading to necrosis, the central core being surrounded by an areola of acute inflammation; that this core is separated by a process of sloughing and so got rid of, the resulting ulcer speedily healing, and leaving a depressed scar which, when occur-

ring about the legs, may become pigmented. Though a self-limiting disease locally, it is nevertheless capable of being inoculated elsewhere in the same individual, both through a breach of surface and also by simple contact of the discharges with the skin, the micro-organism apparently entering by a hair-follicle. This auto-inoculability of boils is apt to be overlooked.

Conditions of debility, presumably by lowering resistance, predispose to boils; the subjects of diabetes are especially prone to them, the saccharine state of the blood or secretions seeming to be particularly favourable to growth of the specific germ.

Treatment.—Boils ought never, unless in very exceptional circumstances, to be poulticed. Poulticing, although it may relieve the pain of the existing boil, is prone to be followed by more boils in the area sodden by the heat and moisture. Neither should boils be incised or squeezed. The only exception to the rule of not cutting is in the case of boils occurring in the scalp or in the axilla. In the former situation, unless opened early, they are apt, especially in young children, to burrow and cause troublesome abscesses; in the latter situation boils tend to be very indolent and painful, and do not readily break through the lax integuments.

In any situation in which the boil is liable to be irritated by pressure or clothing, it is sometimes a good plan to cover the part with a circle of wash-leather spread with soap plaster, and having a small hole cut in its centre corresponding to the apex of the boil. When a boil opens, the discharge must be kept from soiling the adjoining skin, and the patient must be warned against touching the skin elsewhere with pus-soiled fingers. The parts must be frequently cleansed with 1:1,000 corrosive sublimate lotion, powdered with boric acid, and covered with a dry, absorbent antiseptic dressing. A threatening boil may often be aborted by touching the little initial itching or vesiculated papule with some penetrating antiseptic, as iodine tincture, or by painting it with collodion. A very successful method is to drill slowly into the centre of the papule with a pointed pencil of hard wood dipped in pure carbolic acid. The point of the pencil should penetrate at least an eighth of an inch, and should be frequently recharged with the acid during the drilling process; the pain is trifling. In this way, in a severe attack of furunculosis, boil after boil may be aborted and the attack brought to an end. In obstinate chronic furunculosis, excellent results have occasionally attended treatment conducted on Wright's method of exalting the opsonic index of the blood by injections of killed cultures of the patient's pyogenic micro-organisms. An autogenous vaccine ought to be used wherever

possible, beginning with a dose of fifty millions and working up to three hundred millions of organisms.

In severe cases, change of air may be necessary.

PEMPHIGUS CONTAGIOSUS (PYOSIS MANSONI)

Geographical distribution.—*Pemphigus contagiosus* is very common in South China during the hot weather; in some years it may even be described as epidemic. It is perennial in the Straits Settlements, and it is known in Ceylon, Madras, in North Queensland, Japan, and America. European children are more prone to it than native children; European adults are by no means exempt, but the native adult is rarely affected.

Etiology and pathology.—Like *impetigo contagiosa*, this is undoubtedly a germ disease, caused by streptococci and staphylococci. Manson originally found a diplococcus in the epidermis and in the fluid of the blister.

Symptoms.—*Pemphigus contagiosus* closely resembles certain forms of the *impetigo contagiosa* of temperate countries, and is probably a variety of this class of skin disease. The individual lesions, as can readily be ascertained by inoculation experiments, begin as minute erythematous specks, which rapidly proceed to the formation of vesicles, bullæ, or even large pemphigus-like blisters.

Pemphigus contagiosus may occur in almost any part of the body. In young children it is usually diffuse; in adults it is mostly confined to the axillæ and crutch.

Diagnosis.—Absence of constitutional symptoms, or of a history of such, distinguishes pemphigus contagiosus from chickenpox. Absence of trichophyton elements and of a well-defined, slightly raised, festooned, and itching margin together with the presence of large blebs and scaling of the epidermis, distinguishes it from ordinary forms of body ringworm—a disease with which, when occurring in the armpits and crutch in adults, it is frequently confounded.

Treatment.—Cleanliness, the frequent use of a bichloride-of-mercury lotion (1 : 1,000) and a dusting-powder of equal parts of boric acid, starch, and zinc oxide, or ammoniated mercury ointment are specially effective. In the school and nursery those responsible for the care of children must be informed of the contagiousness of this unpleasant affection, and measures be instituted accordingly.

CRAW-CRAW AND ULCERATING DERMATITIS

Synonym.—Nodular Dermatitis.

Symptoms.—The term *craw-craw* is very loosely applied.

Emily has described under this name a papulo-pustular skin affection which is common in certain parts of tropical Africa and is often the cause of much suffering to the traveller. It, or a similar disease, is by no means confined to Africa, for it is seen in patients from Ceylon and India, and Manson was at one time very familiar with it in South China. The disease begins as an itching papule, very possibly at the seat of a mosquito-bite. The itching provokes scratching, whereby some form of pyogenic micro-organism is inoculated. Pustulation follows, and is spread over feet and legs by soiled shoes and stockings, and auto-inoculation. In this way an ulcerating, pustulating dermatitis is kept up.

In the exudate of these papules O'Neil found small filaria embryos which resembled the embryo of *Acanthocheilonema perstans*. Brumpt does not believe that these are examples of the embryos of *Onchocerca volvulus*, as has been affirmed. Possibly they are the same as the microfilaria described by Macfie (*see* p. 788).

Diagnosis.—The hard, horny papules of crawl-crawl have to be differentiated from scabies, which is common in African natives.

Treatment.—Emily describes a very efficient treatment. Pustules are opened, crusts removed, and ulcers scraped. Boric-acid powder is then dusted freely on the parts after a thorough scrubbing with sublimate lotion (1 : 1,000); boricated vaselin is applied on lint, and this is covered by absorbent cotton and a bandage. The dressings are not disturbed for a week, when the parts will be found soundly healed. Similar auto-infective diseases, so common in the tropics, may be treated by prolonged soaking in a warm carbolic-acid lotion (1 : 20), followed by dry dressing with boric powder. Infected slippers, shoes, and stockings should be destroyed.

III. FUNGOUS DISEASES

PRICKLY HEAT

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to the heat of tropical climates.

According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells of which, in consequence of their being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts.

Etiology.—To E. C. Smith of the Medical Research Institute, Lagos, we are indebted for a description of what appears to be the true etiology of prickly heat. In scales obtained from the lesions

he has been able to demonstrate yeast-like budding forms and branching mycelium of a species of *Monilia*.

Tubes of Sabouraud's medium are sown with three or four fragments of scales and maintained at room-temperature. Within six days the fungus appears as an opaque, creamy-white growth. Occasionally a variety is encountered which produces a red colour. In order to obtain it in pure culture, frequent subinoculations are necessary. Microscopically the pure cultures are composed almost entirely of budding forms, staining by Gram. Occasionally short mycelial filaments are encountered.

In scales these yeast-cells can be demonstrated by Gram's method.

Superficial application of cultures to the human skin reproduce the natural disease. A piece of lint 1 in. in diameter is moistened with a thick emulsion of a twenty-four-hour agar growth applied to the shaved skin and maintained in close contact by adhesive plaster. The incubation period is about four days. The area is then found to be covered with minute sudaminal, or herpetic-like vesicles. In the scales collected from the surface of these vesicles the fungus can be demonstrated as well as in the superficial parts of the hair follicles.

The lesions are probably produced by two factors; the mechanical factor is supplied by the irritation produced by a foreign body, the toxic by the fungus itself. This combination produces a progressive oedema of the cells in the vicinity. The portion of the hair-follicle which passes through the epidermis is involved.

Nearly every European in the tropics suffers from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized in this respect, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, in them prickly heat is not a grave affair. It is otherwise in the case of the invalid, of delicate sickly children, of hysterical and, especially, of parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter. Prickly heat is also a common though indirect cause of boils; for the breaches of surface following on the scratching it induces afford many opportunities for invasion by the micro-organisms of furuncular disease.

Prickly heat consists of a miliary-like eruption, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin the feeling as if thickly sprinkled with grains of sand. The eruption may keep out for months on end, becoming better or worse accord-

ing to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching—nothing more certainly than a cup of hot tea or a plate of hot soup. Long drinks, exposure to the hot sun, close rooms, warm clothing, all aggravate the distress. Sometimes the little vesicles pustulate, doubtless from micrococcus infection. As soon as the weather becomes cool the eruption and the irritation quickly subside.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration—particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. Soap should not be used in the bath. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a “Dutch-wife”—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Afridol soap (Bayer), containing oxymercurio-toluylate of sodium, in which mercury is in non-ionisable form, can be recommended as a preventative and a curative measure in prickly heat. The soap is powerfully germicidal and should be used twice daily with warm water. A firm lather should be produced in warm water and applied to the affected parts. The lather should be left to dry on the skin for a quarter of an hour so that it can exercise its full effect, after which time it can be thoroughly washed off. When used as ordinary soap it acts as a preventative against prickly heat. Every bath-room in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts of boric acid, oxide of zinc, and starch. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults. A simple precaution of this sort saves much suffering both from prickly heat and from epiphytic skin disease.

The frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommends the inunction of a mixture of almond oil and lanolin in the proportion of 8 to 1 and scented according to fancy. Some consider thin flannel a better wear than cotton or linen as a preventive of prickly heat. Sometimes the following powder, gently rubbed in for five or ten minutes with a damp sponge, will cure bad patches: Sublimed sulphur, 80 parts; magnesia, 15 parts; oxide of zinc,

5 parts. Lotions of calamine, with or without hydrocyanic acid, or of carbolic acid, relieve the itching temporarily.

MYCETOMA

Synonyms.—Madura Foot ; Pseudactinomycosis.

Definition.—A fungous disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body. It is characterized by enlargement and deformity of the part ; an oily degeneration and general fusion of the affected tissues. The disease runs a slow course, is never recovered from spontaneously, and, unless removed, terminates after many years in death from exhaustion.

History and geographical distribution.—It was first described by Kämpfer in 1712. Subsequently it was confused with tuberculous disease. Carter, from 1865 to 1874, furnished the information upon which modern descriptions of the disease are based. Much further information has since been supplied by Bouffard and Brumpt.

In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name “ Madura foot ” by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. In recent years we have had accounts of its occurrence with some degree of frequency in Senegambia, Somaliland, Algeria, Egypt, the Sudan, Madagascar, Cochin China, Italy, the United States, and South America. It is probable that, in time, forms of mycetoma will be found to be endemic in many warm countries in which they have hitherto escaped recognition.

Symptoms.—Mycetoma begins usually, though by no means invariably, on the sole of the foot. The first indication of disease is the slow formation of a small, firm, rounded, somewhat hemispherical, slightly discoloured, painless swelling, perhaps about $\frac{1}{2}$ in. in diameter. After a month or rather more, this swelling may soften and rupture, discharging a peculiar viscid, syrupy-looking, oily, slightly purulent, sometimes blood-streaked fluid holding in suspension certain minute, rounded, greyish or yellowish particles often compared to grains of fish-roe. In other examples of the disease the particles in the discharge are black, having the size and appearance of grains of coarse gunpowder. Sometimes these particles are aggregated into larger masses up to the size of a pea. In time, additional swellings, some of which break down

and form similar sinuses, appear in the neighbourhood of the first, or elsewhere about the foot. (Fig. 169.) The sinuses are mostly permanent, healing up in a very few instances only. Gradually



Fig. 169.—Mycetoma of about two years' standing. (After Legrain.)

the bulk of the foot increases to perhaps two or three times its normal volume (Fig. 170). There is comparatively little lengthening of the foot; but there is a general increase in thickness, so that

in time the mass comes to assume an ovoid form, the sole of the member becoming convex, the sides rounded, and the anatomical points obliterated. The toes may be forced apart, bent upwards at the tarso-phalangeal joints, or otherwise misdirected, so that when the foot is placed on the ground the toes do not touch it. The surface of the skin is roughened by a number of larger or smaller, firmer or softer hemispherical elevations, in some of which the orifices of the numerous sinuses open.

The discharge issuing from the sinuses differs in amount in different cases, and from time to time in the same case; whether profuse or scanty, it always exhibits the same oily, mucoid, slightly purulent appearance, and may stink abominably. With a very few

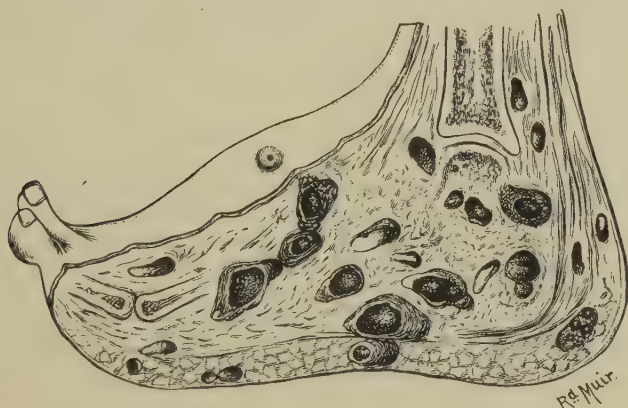


Fig. 170.—Section of a Madura foot. (T. R. Lewis.)

exceptions it contains either the grey or the black grains already referred to; rarely, similar bodies of a reddish or pink colour.

To the touch the swollen foot feels somewhat elastic, and does not readily pit on pressure. The sensibility of the skin is preserved. Although complained of in some instances, severe pain is rarely a prominent feature. The principal complaint is of inconvenience from the bulk and weight of the mass, and, in advanced cases, of the uselessness of the limb for locomotion. In time the foot is no longer put to the ground, different unnatural styles of progression being adopted by different patients.

As the foot enlarges, the leg atrophies from disuse; so that in the advanced disease an enormously enlarged and misshapen foot, flexed or extended, is attached to an attenuated leg consisting of little more than skin and bone. In some cases the tibia or, if the hand is the seat of invasion, the bones of the forearm are

involved; in others the disease at first may be confined to a toe, or a finger, or other limited area. In a very few instances the seat of the disease is the knee, thigh, jaw, or neck. Unless the case be one of actinomycosis, the internal organs are never specifically implicated, either primarily or secondarily. The lymphatic glands likewise, although they may be the subjects of adenitis from secondary septic infection, are very rarely involved.

After ten or twenty years the patient dies, worn out by the continued drain, or carried off more suddenly by diarrhoea or other intercurrent disease.

Etiology. Classification.—The tropical forms of mycetoma were formerly classified according to the colour of the mycotic particles in the discharge. Thus we had the white or ochroid, the black or melanoid, and the red forms of mycetoma, the last being a very rare variety. Brumpt's investigations have made possible a classification more scientific than this crude clinical one; the latter, therefore, has to be abandoned.

This authority distinguishes eight different kinds of mycetoma, as follows:

i. ACTINOMYCOTIC MYCETOMA

Caused by the ray-fungus, *Discomyces bovis* (Harz, 1877). Actinomycosis has a world-wide distribution and is a common disease of cattle. It destroys bone by erosion and spares only nerves and tendons. The pus from the affected region contains small yellowish granules ("sulphur grains") of irregular shape, attaining at most 0.75 mm. in diameter. They are soft and consist of an inextricable felted mass of mycelium. The threads are radially arranged at the periphery of the grain, and their free extremity widens into a bulbous, club-like termination (10–20 μ long by 8–10 μ wide). These clubbed ends have been looked upon by several authors as forms of degeneration.

ii. VINCENT'S WHITE MYCETOMA

Caused by *Discomyces maduræ* (Vincent, 1894). This kind of mycetoma is common and widely distributed. It has been observed in Algeria, in Abyssinia, in Somaliland, in Cyprus, in India, in the Argentine, and in Cuba.

Unlike *D. bovis* and other mycetoma-producing fungi, it does not destroy bone, and does not seem to act directly on the general health of the patient, though ultimately and indirectly it may bring about cachexia.

The grains formed by *Discomyces maduræ* vary in size from a pin's head to a pea. They are of a yellowish-white colour, present a mulberry-like surface, are soft and easily crushed. Their mode of growth is absolutely characteristic. The grain throws out from its periphery radiating filaments. The crown of amorphous rays round the grain is typical.

iii. NICOLLE'S WHITE MYCETOMA

Caused by *Sterigmatocystis (Aspergillus) nidulans* (Eidam, 1883). So far, only one case has been observed, by Nicolle and Pinoy, in Tunis, but probably it occurs in many places, the parasite *S. nidulans* being widely distributed. Primary infection probably takes place from barley grain. The grains formed by this fungus may also attain the size of a pea, but they

differ from those of *Discomyces maduræ*, inasmuch as they are more or less spherical and present a smooth surface.

In this form of mycetoma the bones are attacked and destroyed.

iv. BOUFFARD'S BLACK MYCETOMA

Caused by *Aspergillus bouffardi* (Brumpt, 1906), and discovered by Bouffard at Djibouti, Somaliland. The grains are quite characteristic. They are black in colour and vary in size from a pin's head to that of No. 1 shot. They present a mulberry-like surface which is smooth and glossy, the structure consisting of a coiled-up mass. Maceration in water for about twenty-four hours causes the grain to unfold, while section shows that the grain is composed of a densely felted mycelium of a silvery-white colour, with a peripheral zone of irregularly moniliform threads having terminal chlamydospores cemented together by a dark-brown interstitial substance.

This kind of mycetoma appears to be more amenable to treatment. Bouffard's and Bovo's cases were radically cured by curettage. In Bovo's case a secondary extension to the groin lymphatics of the affected side had suggested the diagnosis of melano-sarcoma.

v. CARTER'S BLACK MYCETOMA

Caused by *Madurella mycetomi* (Laveran, 1902). This mycetoma has a very wide distribution. It has been observed in Italy, in Africa (Senegal, French Sudan), and in India.

The grain formed by *Madurella mycetomi* is dark-brown or black in colour. It measures 1 to 2 mm. in diameter, is hard and brittle; its surface is irregular and frequently presents pointed eminences which differentiate it from the larger and smooth grains of *Aspergillus bouffardi*. The grain is composed of white threads, always over 1 μ in diameter and attaining at times 8 to 10 μ , which secrete a dark-brown substance that cements them together. Sometimes, on account of unfavourable conditions, certain lobes of the fungus separate from the rest of the colony and become independent grains. This mode of vegetation, characteristic of the species, gives to the lesions a typical rosette-like appearance.

In a second species, *M. tozeuri* (Nicolle and Pinoy, 1908), described in South Tunisia, the mycelial elements follow the course of the smaller blood-capillaries.

vi. BRUMPT'S WHITE MYCETOMA

Caused by *Indiella mansonii* (Brumpt, 1906). This form was described from a specimen of Indian origin in the museum of the London School of Hygiene and Tropical Medicine.

The grains peculiar to this form are hard, white, and very small, varying in size between $\frac{1}{8}$ and $\frac{1}{4}$ mm., and having a lenticular shape. Some are bean-shaped and flat. To study their structure it is necessary to boil them first in a solution of caustic potash. The hyphal threads are large and closely set, but without any cementing substance between them. The periphery of the grain contains numerous large chlamydospores having thick walls and being full of protoplasm.

The grains of *Indiella mansonii* are always numerous within the inflammatory tissue. The latter is brownish and is not surrounded by a well-marked sheath of connective tissue as in other mycetomas. It contains numerous polymorphonuclear cells, a few lymphocytes, and some macrophages.

vii. REYNIER'S WHITE MYCETOMA

Caused by *Indiella reynieri* (Brumpt, 1906), originally described by Reynier from a specimen in Paris; a second case has been recorded from Greece.

The grains may attain 1 mm. in diameter; they are soft, white, and consist of a coiled-up strand which gives them a peculiar appearance resembling the excrement of earthworms. They are made up of a dense felting of hyphal threads, the peripheral branches of which usually terminate in chlamydospores divided into two or three compartments. The hyphæ are bound by a scanty cement, which is easily dissolved out by boiling in caustic potash.

viii. BOUFFARD'S WHITE MYCETOMA

Caused by *Indiella somaliensis* (Brumpt, 1906). This form is perhaps even more common in India than Vincent's white mycetoma. Bouffard has found it twice in Somaliland.

Indiella somaliensis is a most destructive fungus. In a foot examined by Brumpt all the muscles, tendons, and bones had been replaced by sclerosed tissues more or less homogeneous and presenting numerous sinuses full of yellowish grains clustered together like fish-roe, and many small inflammatory nodules containing one or more grains.

The grains vary in colour from white to reddish-yellow; they are small, smooth, and attain on an average about 1 mm. in diameter. They are spherical when single, but polyhedral from reciprocal pressure when clustered in masses.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones in parts have entirely disappeared; where their remains can still be made out the cancellated structure is very friable, thinned, opened out, and infiltrated with oleaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a cavity an inch or more in diameter. Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties of mycetoma this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less stuffed with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. An important feature is a sort of arteritis obliterans, or extensive proliferation of the endothelium of the arteries, and, according to Vincent, a thickening of the adventitia of the vessels as well as of the capillaries in the more affected areas.

Treatment.—The only effective treatment, in the case of implication of a considerable part of the foot or hand, is amputation. This must be performed well above the seat of the disease; for it must be borne in mind that the long bones may be implicated as well as the small bones, and that, unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised with success. Potassium iodide in large doses has been found beneficial in certain forms of the disease.

Mossy Foot

The term "mossy foot" was applied by Wolferstan Thomas to a papillomatous condition of the feet and legs which is found occasionally in natives of the Amazon valley and its tributaries.

A similar condition has been described from Honduras. The foot and ankle are covered with dense warty-looking outgrowths resembling minute barnacles; the individual papillomata are dense and wart-like, but vascular and painful. In general appearance the condition has been compared to dry moss growing on rocks. (Fig. 171.)

The sole of the foot usually escapes. The disease is infective, and autoinoculation from one limb to another may apparently take place. Starting as a vesicle, the growth slowly extends from the dorsum to the hinder part of the foot, and is said to take ten years to develop fully. It can be inoculated into the nose in rabbits, and produce in them a verrucoid mass at the site of inoculation.

Etiology.—The disease is said to be due to an infection of the skin with a fungus, *Phialophora verrucosa* Thaxter, 1915, which was specially studied by Pedroso and Gomes in Brazil in 1920. It can be cultured on ordinary media, and forms a brownish-black growth. Stab-cultures in ascitic agar and serum form, in the depth of the medium, nodules analogous to those in the tissues.

On these media, chlamydospores $8-15\mu$ in diameter, as well as conidia, are produced, and sometimes aerial hyphæ develop.

According to Medlar, yeast-like cells can be seen in sections of the tissues.

Treatment.—In Thomas's experience, the best treatment is the actual cautery.

BLASTOMYCOSIS

This term is used to indicate lesions, other than mycetoma, produced by the proliferation of certain yeast-like fungi in the tissues. Normally these fungi are either saprophytic or live as parasites on animals or plants, and appear to be especially abundant

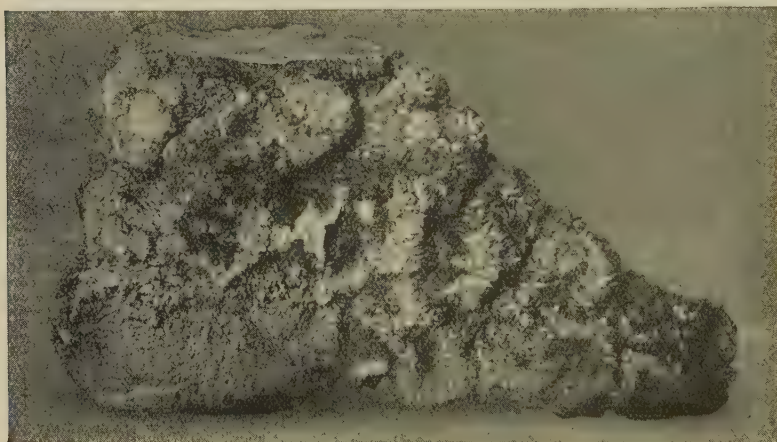


Fig. 171.—Mossy foot. (By courtesy of Wellcome Bur. Sci. Res.)

in tropical countries. Doubtless they get access to the human tissues through some wound or breach of surface. The following clinical types have been recognized :

1. *Cutaneous.*—Patches, of various dimensions, of small warty excrescences with minute abscesses or encrusted ulcers, especially at the periphery of the patch.

2. *Oral.*—Lesions resembling the foregoing, which develop in or spread to the mucosa of the mouth and throat, and eventuate in deep ulceration and perhaps fatal destruction of the part. A from occurs on the tongue, leading to hypertrophy of the filiform papillæ, and causing a condition known as *lingua nigra*. The organism is known as the *Cryptococcus linguæpilosæ*; it has a

double contour, is composed of oval yeast-like cells and mycelia elements, and can be cultivated on maltose-agar.

3. *Coccidial*.—The skin lesions are similar to those of type 1, but usually larger and coarser. The viscera becoming involved, death ensues. In the affected tissues peculiar round bodies, 3μ to 80μ in diameter, many of them containing a multitude of spores, are a feature.

4. *Gluteal*.—There is extensive brawny thickening of one or both gluteal regions, the superjacent skin being thickened and coarse, and perforated with the openings of many communicating sinuses. The condition is apt to be regarded as an aggravated form of fistula in ano.

5. *Pulmonary*.—A parasite, the *Cryptococcus capsulatus*, allied to *C. farciminosus* of the horse, has been demonstrated in the epithelial cells of the lung by Darling. The disease it produces resembles in many respects kala-azar, and is accompanied by splenomegaly, anæmia, irregular pyrexia, and leucopenia. Three cases have been described in Panama.

6. *Sporotrichosis*.—Gumma-like swellings in limbs or trunk, which enlarge and ultimately break down, leaving deep ulcers, due to an organism, *Sporotrichum beurmanni*, which usually exists saprophytically, and gains entrance to the body through an abrasion of the skin or oesophagus. Occasionally the organism may be demonstrated in the blood; the lymphatics, eye, oral cavity, periosteum, muscles, or viscera may become involved. In the discharges and tissues the parasites are scanty, so that the mycotic nature of the disease can be made out only from cultures.

Sporotrichum beurmanni can be isolated from the tissues by aspiration and insemination on to Sabouraud's medium. The parasite occurs in wild rats in Argentina and Brazil, while a similar disease, apt to be mistaken for epizootic lymphangitis, occurs in horses and mules in Madagascar (Carougeau).

It appears to be a common parasite in nature, and is found on vegetables, and often in the oral cavities of healthy subjects.

The parasitic elements are very scanty in the pus, and in mycelial elements are seen either in sections or in cultures. Individual parasitic elements are often found engulfed by phagocytes.

Pathology.—At the borders of the ulcerated tissue there are accumulations of inflammatory cells and other elements, especially giant cells, which include the organisms.

Diagnosis.—Usually these lesions in the first instance suggest syphilis or tuberculosis. Specific treatment and absence of reaction to tuberculin and of the tubercle bacillus should lead to a careful search for yeast-like organisms in the discharges or scrapings. Widal and Abrami have found that the serum of

sporotrichosis will agglutinate cultures of the specific organism; while Malvoy and Ricketts have demonstrated a complement-deviation test in blastomycosis, using old cultures of blastomyces as an antigen.

Treatment.—All forms of blastomycosis are exceedingly chronic and resistant to treatment. Surgical measures are useless, but large doses of the iodide of potassium or of sodium (20–30 gr. three times a day, well diluted) are sometimes effective, and should always be tried and, if found beneficial, continued until cure is well established. In sporotrichosis the tumours can be punctured and injected with potassium iodide 1 : 100, while treatment must be continued for some time after an apparent cure has taken place. The X-rays are at times a useful adjunct.

DHOBIE'S ITCH (TINEA CRURIS) AND PITYRIASIS VERSICOLOR

Etiology and nomenclature.—By the lay public all epiphytic skin diseases—more especially all forms of intertrigo—are spoken of as *dhobie's* (washerman's) *itch*, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned *dhobie*.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-pigmented skins of negroes, Indians, and dark-complexioned Chinese, the patch of pityriasis—contrary to what obtains in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The disease is most commonly seen in young adults, is favoured by excessive perspiration, and especially by flannel underwear, and is rarely seen in the aged.

There are possibly several varieties of fungi involved in the

production of pityriasis; besides *Microsporum furfur*, the best-known is *Microsporum mansonii*, of which a culture in maltose-agar produces black hemispherical colonies, and correspondingly black patches on the affected skin.

The expression dhobie's itch, although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. There are at least two species of parasites which in the tropics are prone to attack those situations, namely a trichophyton—*Epidermophyton inguinale*—and the *Microsporum minutissimum* of erythrasma.

E. inguinale is peculiar to man only; it is not easily cultivated, and grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as powdery growth.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather, especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely, from secondary bacterial invasion, to boils or small abscesses. The crutch, or axillæ, or both, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress. In some cases the clefts between the toes are attacked, giving rise to great itching. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even in the absence of treatment, when the cold season comes round the dermatitis and irritation subside spontaneously. The affected parts then become dry, pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made. The festooned margin is almost conclusive. When doubt exists, recourse to the microscope may be necessary; but, owing to the inflamed condition of the parts, there may be much difficulty in finding fungus elements even when the case is certainly epiphytic. A negative result is, however, not always conclusive against ringworm. The mycelial elements can usually be distinguished in epidermal scales soaked in liquor potassæ.

Treatment.—After a thorough use of soap and water, the application of *Vlemminck's solution* of sulphide of calcium (1 oz. quicklime, 2 oz. precipitated sulphur, 15 oz. water, boiled together in an earthenware vessel till reduced to 10 oz.; the clear sherry-coloured

fluid being decanted after subsidence) every night for three or four times generally brings about a rapid cure. If the parts are inflamed and tender, the solution should be diluted to half- or quarter-strength for the first two applications. A preliminary soothing treatment by lead lotion, or an ichthyol or hazeline ointment, is desirable in such cases. A tincture of the leaves of *Cassia alata* painted on, or vigorous rubbing with the crushed leaves themselves, is equally successful. If these fail, chrysophanic-acid ointment, 20 gr. to the ounce of vaselin, rubbed in twice a day till a slight erythema shows at the edge of the diseased patch, is almost invariably successful. When prescribing chrysophanic acid the physician must be careful to inform the patient of its staining effect on clothes; to warn him to stop its use as soon as the erythematous ring shows, and to be careful not to apply the ointment to the face.

More conveniently, chrysophanic acid may be prescribed in the following form with gutta-percha, and should be painted on with a brush on alternate nights.

Acid. chrysophan.	.	.	.	gr. xx.
Chloroformi	.	.	.	3 i.
Liquor gutta-perchæ	.	.	.	3 i.

An ointment of resorcin 1 dr., salicylic acid 10 gr., benzoic acid 10 gr., lanolin and vaselin 4 dr. each, to be applied twice a day, has been recommended. For the ringworms of the thick-skinned natives, linimentum iodi freely applied, and of double strength, is the best, speediest, and most efficient remedy, but it is too irritating and painful for the European skin.

During treatment the wearing of short cotton bathing-drawers is recommended.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

RINGWORM OF THE FEET (HONGKONG FOOT)

A peculiarly intractable infection of the soles of the feet occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot." This mycotic infection, as identified by Dold, is believed to be a variety of *Epidermophyton inguinale*. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities;

or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface; scaling of the skin with persistent and intolerable itching is a marked feature. Often a mycotic infection of the nails and the palms of the hands is associated with it. A similar condition has been described as occurring in Turkish baths in England by Whitfield. As a preventive measure the application of the following lotion is recommended:

Liq. formaldehyde (40-per-cent.)	3 i.
Acid salicylic	3 i.
Alcohol and water equal parts	3 viii.

Treatment.—The application of Whitfield's ointment is recommended: Salicylic acid 1, benzoic acid 1, coconut oil 12, soft paraffin 16.

Macleod recommends bathing or paddling in sea-water.

RINGWORM OF THE NAILS (*TINEA UNGUIUM*)

This is a mycotic infection of the nails and is a comparatively common, and extremely intractable, condition in Europeans, especially in India and China; it is a singularly persistent infection and may last for twenty years or more. It may occur as an independent affection or secondary to ringworm of the skin, scalp, or beard, and is often found in association with *tinea cruris*. The nails of both hands and feet may be attacked or single ones of each member. The fungus is a trichophyton, usually *Epidermophyton inguinale*; it is never caused by a microsporon.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discoloration, ridging and fissuring of the nail itself, which becomes opaque with a brittle frayed edge. The fungus may pass from the skin over the nail-fold and in this manner reach the matrix.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are placed in liquor potassæ and gently heated. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail debris.

Treatment.—In the early stages when the lunule is attacked the disease may be stamped out by softening the affected portion with liquor potassæ and painting with tincture of iodine or with a 2-per-cent. solution of corrosive sublimate in alcohol, twice daily. When the nail is completely involved, cure is almost impossible

save by extirpation or by evulsion. After removal the thickened nail-bed should be scraped and the matrix dressed with a parasitical ointment :

Acid salicylic	gr. xxx
Ung. hydrarg. ammon.	gr. xv.
Vaseline	$\frac{3}{4}$ i.

The shedding of the nails by application of X-rays is unsatisfactory. Less severe cases are treated by softening the nail-plate by wearing finger-stalls of rubber containing soft soap for a few days ; the softened nail is then scraped down as far as possible with glass, followed each time by the application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodide 1, water 100), which should be kept in position by a loose rubber finger-stall.

TINEA IMBRICATA

Synonym.—Tokelau Ringworm.

Geographical distribution.—The affection is principally met with in the Eastern Archipelago and in the islands of the South Pacific, where it affects a large proportion of the population ; cases have been reported from Central Africa, and it occurs in the interior of Brazil. It has been found to extend westwards as far as Burma, and northwards as far as Foochow and Formosa on the coast of China. Once introduced, it spreads very rapidly in countries with a damp, equable climate and a temperature of 80–90° F. Very high or very low temperatures and a dry atmosphere are inimical to its extension.

Etiology.—On detaching a scale and placing it under the microscope, after moistening with liquor potassæ, a trichophyton-like fungus can be seen in enormous profusion. The parasite evidently lies between epidermis and rete, and by its abundance causes the former to peel up. As the fungus does not die out in the skin travelled over, it burrows under the young epithelium almost as soon as the latter is reproduced. Hence the peculiar concentric scaling and the persistency of the disease throughout the area involved. When the scales are washed off by the vigorous use of soft soap and hot water, the surface of the skin is seen to be covered with parallel lines of a brownish colour—evidently the slightly pigmented fungus proliferating and advancing under the young epidermis.

The parasite, said by Castellani to be of two species, *Endodermophyton concentricum* and *E. indicum*, can be cultured by immersing the scales in alcohol for five to ten minutes and then placing them, one scale to each tube, in glucose broth. After five or ten days the scales, if uncontaminated, are transferred to solid media, and growth takes place in three or four weeks.



TINEA IMBRICATA.

(By permission of Medical Department of Sanitary Government.)

Symptoms.—*Tinea imbricata* may at first be confined to one or two spots on the surface of the body ; usually, in a short time it comes to occupy a very large area. It does not generally affect the soles and palms, although it may do so ; nor is the scalp a favourite site. Baker remarks that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease, as may be seen from Plate XXXII.

An inoculation experiment readily explains the production of the scales, their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with *tinea imbricata*, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter-of-an-inch in diameter—gives way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth ; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from $\frac{1}{8}$ to $\frac{1}{2}$ in. apart. The hair of the scalp is not injured.

Diagnosis.—From *ordinary ringworm*, *tinea imbricata* is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From *ichthyosis* it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for *tinea imbricata* in natives is the free application of strong linimentum iodi ; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic-

acid ointment (20 gr. to the ounce). Clothes should be boiled or burned.

Prophylaxis.—Daniels relates that *tinea imbricata* is a comparatively rare disease in Tonga. This circumstance the natives attribute to their custom of oiling the body with coconut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes whose women oil their bodies it has never been observed, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

PINTA

Synonyms.—Caraate; Mal del Pinto.

Definition.—An epiphytic disease characterized by peculiar pigmented patches on the skin.

Geographical distribution.—Pinta occurs in certain districts in tropical America, especially along the river banks—in Mexico, Central America, Venezuela, Colombia, Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras, and Brazil.

Etiology.—If one of the scales is moistened with liquor potassæ and placed under the microscope, black spores and a white, highly refracting mycelium are found (Fig. 172). The spores are round or oval, measuring $8\ \mu$ to $12\ \mu$ in diameter. Abundant pigment is seen floating in a yellowish fluid in the interior of the spore. The mycelial filaments are short, non-branching, tapering from a broad base to a blunt point by which each filament is attached to a single spore, like the stalk to a cherry. The mycelium measures from $18\ \mu$ to $20\ \mu$ in length by $2\ \mu$ in breadth. The differences in the colour of the patches probably depend on differences in the pigmentation, or kind, of the fungus.

Symptoms.—Pinta commences at one or two points, the rest of the surface of the skin becoming infected in turn by extension or by autocontagion. At first the hands or face, or some other exposed parts, are attacked. The original patch becomes hyperpigmented owing to active pigment-formation, but later it becomes white, red, blue, or black. It gradually increases in size, becoming scurfy and itchy, particularly when the surface is warm. As the patches spread they assume a variety of shapes. Fresh spots



PINTA.

(Photo: Dineen, San Francisco.)

appear in the region of the parent spots, into which, in course of time, they tend to merge, so that ultimately large patches of discoloured skin are formed. (Plate XXXIII.) The palms of the hands



Fig. 172.—Fructification of cryptogamic epiphytes in pinta.
(After Montoya y Florez.)

A, Red pinta ; B, dark-violet pinta ; C, grey-violet pinta ; D, blue pinta.

and the soles of the feet are not attacked. On the scalp becoming affected the hair turns white and thin, and ultimately falls out. When fully developed the disease produces a very grotesque appear-

ance. It is probable that the white patches in a proportion of cases are not epiphytic, as they neither itch nor desquamate; very likely they are ordinary leucoderma, possibly brought about through disturbance of the natural pigmentation by a parasite which subsequently died out. Neither sensation nor the glandular functions of the skin are affected. In consequence of the scratching, the implicated parts may become cracked or ulcerated.

Two types of the disease have been named—the superficial epidermic and the deep epidermic, the former being represented by black and blue patches which spread rapidly, the latter including the red and white patches, apparently involving the rete and deeper layers of the epidermis, spreading more slowly, and, at the same time, being more difficult to cure. The various forms and colours may concur in the same individual; but a given patch, once established, does not change colour.

Pinta is contagious. It attacks both sexes and any age. Unless properly treated it may last for years. Want of personal cleanliness has a great deal to do with the prevalence of pinta in the countries mentioned, for it is seldom met with in Europeans or in prosperous negroes. In some districts it is comparatively rare, while in others nearly the entire population is affected. The patient emits an offensive odour not unlike that of dirty linen. No constitutional disturbance is provoked.

Diagnosis.—This disease is readily diagnosed from leprosy by the absence of anæsthesia in the patches, and by the colour of the spots; from erythrasma, from ringworm, and from pityriasis versicolor by the colour and the microscopic characters of the fungus.

Treatment.—Chrysophanic acid, preparations of sulphur, strong liniment of iodine, and other epiphyticides are indicated. Cleanliness and the destruction of old clothes are indispensable.

TRICHOSPOROSIS

Synonym.—Piedra.

This peculiar disease of the hair is very common in certain districts of Colombia and British Guiana. So far as is known, it is confined to the inhabitants of those countries, of whom a considerable proportion, both male and female, and apparently belonging to all the races represented there, are affected. It is commoner in native women, but has been observed on the eyelashes, beard, and scalp.

The hairs are dotted over at irregular intervals with numerous (1 to 10 or more in a hair 60 cm. in length) minute, gritty nodosities.

These, barely visible to the naked eye, are distinctly perceptible to the touch when the hair is drawn between finger and thumb. The affected hairs are bent and twisted, and tend to produce matting and knotting. The little nodosities—which, though very firm, are not so hard as the name *piedra* (a stone) would indicate, being easily cut through with a sharp knife or scissors—are paler than the hair which they surround, or partly surround, like a sheath. They are situated in the extrafollicular portion of the hair, and vary in number from one to ten or more. When a comb is drawn through the hair, a sort of crepitation is produced, doubtless by the friction against the hard particles.

Etiology.—Under the microscope the excrescences are found to consist of a number of spore-like bodies, *Trichosporum giganteum*, easily made apparent by soaking the hair in liquor potassæ after washing in ether. From mutual pressure the spores, which are twice the size of trichophyton spores and remarkably refringent, are polyhedral, and together form a sort of tessellated mosaic, the elements of which seem to be held together by a greenish soluble cement in which a number of minute bacteria-like rods are incorporated. The shaft of the hair—not eroded or affected in any way—can be seen intact through the encrusting fungus. *T. giganteum* is easily cultivated on ordinary media. It liquefies gelatin in ten or twelve days. The smallest spores measure 2–5 μ , the largest up to 12 μ . *Piedra* is supposed by some to be induced by the mucilaginous hair applications in vogue among the Colombians.

Diagnosis.—Although Juhel-Rénoy has given to *piedra* the name “trichomycose nodulaire,” the condition must not be confounded with trichomycosis nodosa, which is a different affection and common enough on the axillary, scrotal, and face hair in Europe and elsewhere. Neither must it be confounded with trichorexis nodosa, a non-parasitic disease of the hair-shaft, which is split up at different points into brush-like bundles of fibres, and is thus easily fractured; nor with moniliform hair, a congenital, hereditary, and non-parasitic condition.

Treatment.—Cleanliness, the free use of soap, and the application of some epiphyticide should suffice for cure; but should such means fail, doubtless shaving the scalp would be effectual.

TRICHOMYCOSIS

Synonyms.—Trichonocardiasis; Trichomycosis nodosa.

Trichomycosis is a fungous disease of the hair in many ways resembling *piedra*, and common in Central Africa. It may produce

skin irritation and staining of the clothes. The shafts of the hairs, more especially those in the axilla, are attacked. The parasite is thought to be *Discomyces* (*Nocardia*) *tenuis* (Fig. 173). The hairs have a beaded or nodular appearance and the deposit may vary considerably in colour. The disease may spread to the skin and cause a severe intertrigo.

Treatment.—The affected hair should be bathed twice daily

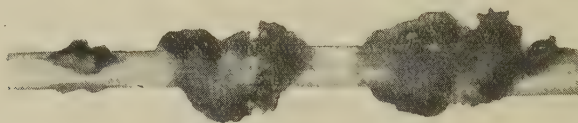


Fig. 173.—Trichomycosis. Human hair, magnified.
(Wellcome Bur. Sci. Res.)

with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. of sulphur ointment.

IV. SKIN DISEASES CAUSED BY ANIMALS

THE CHIGGER, OR SANDFLEA

This insect, formerly confined to the tropical parts of America (30° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example.

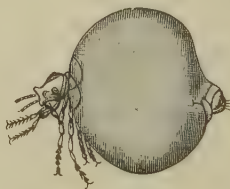


Fig. 174.—Chigger, impregnated female. × 10.
(Blanchard.)

As a cause of suffering, invaliding, and indirectly of death, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian coolies there, by whom it has been introduced into India.

The chigger (*Tunga penetrans*) is not unlike the common flea (*Pulex irritans*) either in appearance or, with one exception, in habit. It is some-

what smaller in size (1 mm.), the head being proportionately larger and the abdomen deeper than in the latter insect. In colour it is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impregnated, the female, like the male, is free, feeding intermittently as opportunity offers. So soon as she becomes impregnated she avails herself of the first warm-blooded animal she encounters to burrow diagonally into its skin, where, being well nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea (Figs. 174, 175). The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by



Fig. 175.—Section of female chigger in the stratum lucidum of the skin.
(Fülleborn, *Arch. für Schiffs-und Tropenhyg.*)

the flea on entering the skin. When the eggs are mature they are expelled and fall on the ground. In a short time a thirteen-ringed larva is hatched out from each egg. This larva presently encloses itself in a cocoon, from which, in eight or ten days, the imago emerges.

Generic name of the chigger.—Until recently known as *Sarcopsylla* Westwood, 1840, or *Dermatophylus* Lucas, 1839, the sandflea, as Rothschild pointed out, should bear the generic name of *Tunga*, as it was figured as *T. penetrans* by Jarocki in 1838. It becomes, therefore, by the law of priority, *Tunga penetrans*.

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus forms around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates and the chigger is expelled, leaving a small sore which may be infected by some

pathogenic micro-organism, as the bacterium of phagedæna or of tetanus, with grave consequences.

Being nearest the ground, the feet are the part most commonly infested by chiggers. The soles (Fig. 176), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means exempt; the scrotum, the penis, the skin around the anus, the thighs, and even the

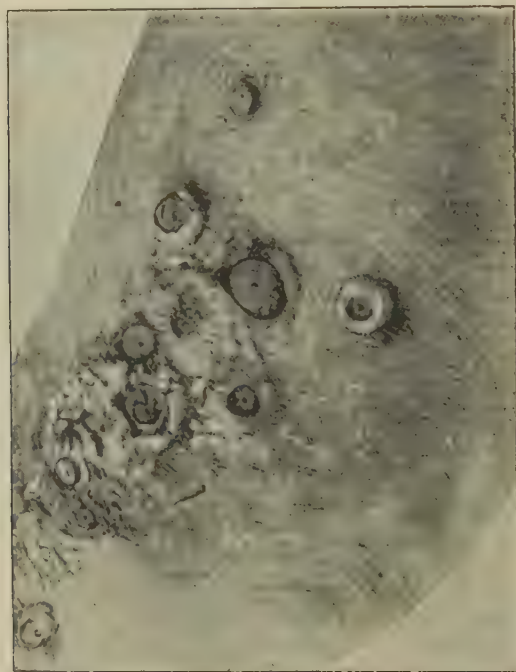


Fig. 176.—Chiggers in sole of foot. (Photo: Dr. C. W. Daniels.)

hands (Fig. 177) and face, are often attacked. Usually only one or two chiggers are found at a time; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and the accumulation of dust and debris prevented. The housing of cattle, pigs, and poultry demands the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, or similar

insecticide, and walking bare-footed must be avoided. Bathing must be practised daily, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little opera-



Fig. 177.—Chigger lesions of hands and feet.
(Photo : Dr. C. W. Daniels.)

tion. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired; the floors of huts and tents may be sprayed with insecticides and naphthaline, and native tobacco dusted inside boots or shoes. Balfour recommends that the feet be rubbed thoroughly with

a mixture consisting of 5 drops of lysol or liq. cresoli sap. in 1 oz. of vaselin. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

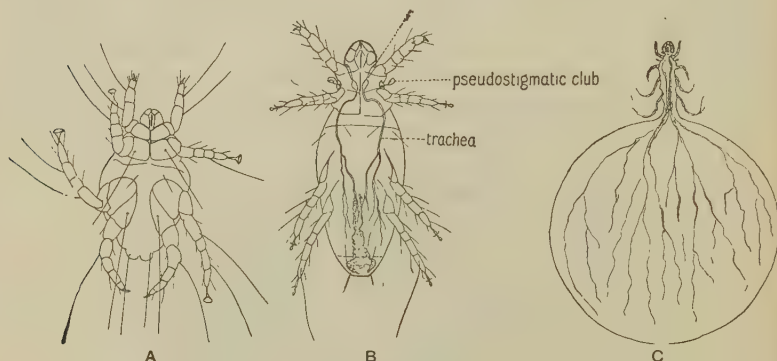


Fig. 178.—*Pediculoides ventricosus*. $\times 80$. (After Alcock.)

A, Male; B, adult female; C, pregnant female with brood-sac.

ACARINE DERMATOSIS

Several forms of mites inhabiting sugar, grain, or copra may live as temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most familiar of these is "grocer's itch," set up by mites of the genus *Glycophagus*, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to a *Tyroglyphus*. "Grain itch," an urticarial and papular eruption of the exposed parts of the body, is caused by *Pediculoides ventricosus* (Fig. 178, A, B, C) in those who handle grain, cotton-seed, or beans. The presence of these mites gives rise to a severe pruritus. Preventive treatment consists in the application of beta-naphthol ointment (5-per-cent.), and the employment of dilute carbolic acid to kill off the mites.

Section VIII.—LOCAL DISEASES OF PROBLEMATICAL NATURE

CHAPTER XL

CLIMATIC BUBO—RHINOSPORIDIOSIS—AINHUM— BIG HEEL

CLIMATIC BUBO

SCHUEBE applied the term "climatic bubo" to a type of adenitis not uncommon in tropical climates. So far as available statistics show, the disease is especially prevalent among the crews of warships on the eastern coast of Africa. It occurs also in the Straits of Malacca, in China, in the West Indies, Japan, the Mediterranean, and probably in many other places, including, perhaps, in a minor degree, Europe. It appears to be epidemic at times in certain places. Rost, who observed seventeen cases on board a training-ship, believed that the infection is acquired from sexual connexion with native women. Hanschell considers that, if carefully looked for, a small ulcer is visible on the corona of the penis, which heals up after a few days. The adenitis does not commence till after the primary lesion has healed. The affection is comparatively common in European men in the tropics, and is seldom, if ever, seen in European women. Hanschell has never seen a case in a circumcised man. According to de Bellard the disease can be reproduced in monkeys by inoculation.

Symptoms.—The incubation period is three to four weeks after coitus. The disease generally commences with fever of a remittent type in association with inflammatory swelling, usually of a subacute character, of the groin glands. The oblique inguinal glands are those most frequently affected, but at times it is the crural glands that are attacked. Sometimes both groins are affected, sometimes only one, sometimes one groin after the other. The affected glands slowly or more rapidly enlarge to the size of a hen's egg, or even larger. After several weeks, it may be months, the swelling gradually subsides. Occasionally the periglandular connective tissues inflame, the integuments

become adherent, and suppuration ensues. If the suppurating glands be freely excised, the parts readily heal; but if they are left alone, or inefficiently treated, fistulous tracks form which may take a very long time to heal. Sometimes, however, if too much lymphatic tissue is removed, an elephantoid condition of the leg on the affected side may develop. This is a grave objection to surgical interference, added to the fact that secondary septic infections are very liable to ensue.

Diagnosis has to be made from venereal bubo, filarial adenitis, and plague. None of these diseases should cause any real difficulty.

Treatment should consist in rest and soothing applications during the more acute stage. After pain and tenderness have subsided, graduated elastic pressure should be applied; X-rays have been recommended. Concurrent malaria would call for quinine; syphilis, for mercury or the iodides.

Hanschell records dramatic results following the adoption of protein-shock therapy by intravenous injection of mixed typhoid-paratyphoid vaccine, commencing with 100 million and gradually increasing to 400 million organisms, the injections being given every third day. Two, or rarely three, injections are necessary. The buboes dry up and the surrounding induration quickly disappears. If suppuration is extensive the cavity should be aspirated, never incised. Open lesions should be treated with applications of eusol.

RHINOSPORIDIOSIS

Definition.—A disease due to a yeast-like organism, *Rhinosporidium seeberi*, which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, the conjunctiva, lacrymal sac, and uvula.

History.—*R. seeberi* was first described in the Argentine (1896), and considered to be a protozoon allied to *Coccidium*. Subsequently it was found in nasal polypi by O'Kinealy in 1903, when the organism was described by Minchin and Fantham. Ashworth (1923) has recently shown that the organism is probably a yeast, or phycomycete.

This parasite has now been recorded from India, Ceylon, Argentina, and the United States.

Etiology.—*Rhinosporidium seeberi* (Wernicke 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about 6μ in diameter, with a chitinous envelope, vacuolated cytoplasm, and a vesicular nucleus containing a karyosome. (Fig. 179, A, B.) When fully-grown, the cyst, or sporangium, may measure 0.25–3 mm. in diameter, but when half-grown the

nucleus commences to divide by binary fission till thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully formed sporangium (Fig. 179, c) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then spread into the connective tissues via the lymph channels, and on their reaching suitable spots the trophic stage at once begins and the cycle is repeated.

Attempts at cultivation of the parasite have proved to be partially successful in Ashworth's hands, and multiplication of the spores took place, but very slowly, on Sabouraud's medium.



Fig. 179.—*Rhinosporidium seeberi*. (After Ashworth; by permission of Roy. Soc. of Edin.)

a. Trophic stages. b. Section of a stage with 64 nuclei, 24 of which lie in this section. c. Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickened annulus round the pore.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, *R. equi*, in the nasal cavities of the horse is suggestive.

Treatment consists in removing the polypi from the nares by means of a wire snare. Medical treatment would not appear to be indicated, although Wright has reported that the tumours disappear after intravenous injections of tartar emetic.

AINHUM

This is a disease of a very peculiar character, affecting the toes, particularly the little toes, of negroes, East Indians, and

other dark-skinned races, both in the Old and the New World. The name, derived from the Nago dialect, means "to saw or cut."

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once started, deepens and extends gradually round the whole circumference of the toe. As it deepens—it may be, though not necessarily, with an amount of ulceration—the distal portion of the member is apt to swell to a considerable size, as if constricted by a ligature. (Fig. 180.) There is little or no pain, although there may be inconvenience from the liability to injury to which the



Fig. 180.—Ainhum.

dangling and now everted toe is exposed. In the course of years the groove slowly deepens, and finally the toe drops off or is amputated. The groove may either correspond with a joint or may be formed over the continuity of a phalanx. In rare instances, after the two distal phalanges have dropped off or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affected; very rarely is the third, or second, or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Ainhum is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that

the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of the papillary layer of the skin, together with a band of fibrous tissue, more or less intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might be tried. When troublesome, the affected toe should be amputated.

BIG HEEL, OR ENDEMIC HYPERTROPHY OF THE OS CALCIS

Maclean described a peculiar form of enlargement of the os calcis which he observed at Kaziankor, Gold Coast, among Fantis and Kroos. The disease begins somewhat suddenly, being preceded by fever, and attended by pain and tenderness which reach their maximum in about a month, gradually diminishing during the succeeding one or two months. Concurrently with the pain a swelling of the external surface of the os calcis, rarely of the other tarsal bones, makes its appearance.

Maxwell has reported a similar condition in natives of Formosa. As in Maclean's cases, the patients were young adults from 20 to 25 years of age.

Section IX.—TECHNIQUE

CHAPTER XLI

TECHNIQUE OF INJECTIONS IN THE TREATMENT OF TROPICAL DISEASES

INTRAVENOUS THERAPY

Preparation of the patient.—The patient should preferably be placed in a sitting position, with his arm resting on a board or other firm object. The median-basilic or the cephalic vein at the bend of the elbow usually offer the best sites for injection, both being easily visible and situated close beneath the skin. The veins are rendered prominent by instructing the patient to clench the hand and by constricting those in the upper arm, which is best done by means of a piece of moderate-sized rubber tubing ($\frac{1}{4}$ in. in diameter), clipped by a Spencer Wells or tongue forceps, so that the pressure can be released subsequently with ease. In certain cases the distended vein can be felt distinctly under the skin with the examining finger, even when it cannot be seen. Fat subjects often present considerable difficulty, and in these cases it may become necessary to resort to the distended veins on the dorsum of the hand.

The site having been selected, the skin is sterilized by means of a strong solution of iodine, which should be removed by the application of ether or strong spirit.

Method of injection.—The syringe is now filled with the selected drug; this is best done by drawing up the solution from a sterile test-tube or other glass receptacle, care being taken to exclude all air-bubbles.

The needle should be plunged into the vein. Penetration should be effected in two stages, first through the skin, and secondly in an upward direction into the lumen of the vein. When the needle is felt to be inside the vein—usually within $\frac{1}{8}$ in. from the surface of the skin—the plunger should be slightly withdrawn; blood will then well into the barrel. Directly this is seen, the tourniquet should be loosened and the injection steadily made. When it is completed, a finger should be pressed over the site of injection and the needle withdrawn. Great care should be taken not to transfix the vein; in that case the solution is injected into the tissues behind the vessel and may result in inflammatory disturbances, or even abscess-formation.

The syringe and needles.—For most purposes a 10-c.c. Record syringe is satisfactory, though for the injection of serum one of a larger capacity, up to 20 c.c., may be necessary. The type fitted with a peripheral nozzle (Fig. 181) is most suited for intravenous therapy. It is advisable to test the syringe before use by drawing up boiling water, for often the plunger, on becoming overheated, is apt to stick in the barrel.

Success or failure depend to a very great extent on the sharpness or otherwise of the needle. If possible, a new steel-wire needle should be used on each occasion. The size is also important; it is necessary to select a stouter type of needle than is usually utilized for subcutaneous injection. About No. 12 is the most suitable size. (Fig. 182.)

The sterilization of the syringe is an important matter. Whenever possible, a steam sterilizer should be used, and the parts of the syringe taken to pieces and wrapped in lint or cotton-wool. A more practicable method consists in drawing up into the barrel boiling water for the space of three or four minutes. In this manner, not only is complete sterilization obtained, but the process is less damaging to the glass of the barrel and less detrimental to the metal parts.

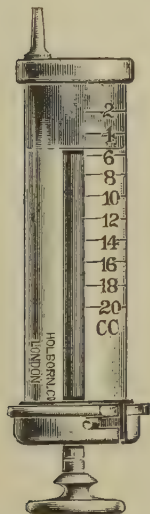


Fig. 181. — Record syringe with lateral nozzle for intravenous injections.



Fig. 182.—Intravenous or intramuscular needle, size No. 12.

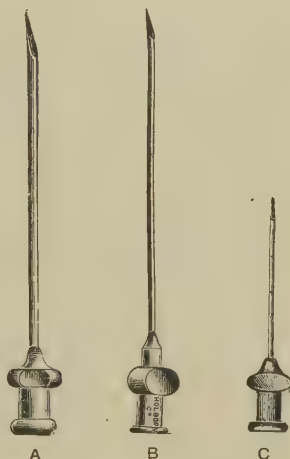


Fig. 183.—Various sizes of exploring, serum, and hypodermic needles.

A, Aspiration needle. B, Intramuscular needle. C, Hypodermic needle, No. 16.

Needles (Fig. 183) keep best if smeared with vaselin, or kept in carbolized oil. Plunging the needle-points into a block of hard paraffin wax will prevent them from rusting.

Drugs employed.—*Antimony tartrate* is being extensively used for the treatment of various tropical diseases. If it is properly prepared, the toxic after-effects are practically negligible; those formerly observed after intravenous injection of the drug were probably due to the large quantity of saline solution (often amounting to a pint or more) which was used for dilution. There are two forms of tartar emetic—the potassium and the sodium salts; the latter is usually preferred by reason of its greater solubility and lesser toxicity.

Potassium-antimony tartrate, $(K_2Sb_2C_8H_8O_{14})H_2O$, is soluble in 7 parts of cold and in 3 parts of boiling water.

Sodium-antimony tartrate, $(NaSbOC_4H_4O_7)2H_2O$, is very soluble in hot

water and in $1\frac{1}{2}$ times as much cold water. It dissolves easily in an equal weight or more of water, the solution being almost neutral, showing a slight alkaline reaction to methyl-orange and a slight acid reaction to methyl-red or litmus, and requiring about the same amount of N/10 acid or alkali to produce neutrality towards the respective indicators. Methyl-red, however, is the indicator most suitable for checking the neutrality.

Tartar emetic is usually made up in a 1- or 2-per-cent. solution, the initial dose being $\frac{1}{2}$ gr. of the salt, working up to a maximum of $2\frac{1}{2}$ gr. for an individual dose. The solution should be made up with freshly distilled sterilized water, preferably with the addition of 5-per-cent. glucose, immediately before use, and injected with a 10-c.c. syringe, the powder being weighed out on the scale—say 1 or 2 gr.—and placed, together with the requisite amount of water, in an Ehrlenmeyer flask, which can then be brought to the boil. It is not advisable to overheat antimony salts, as is commonly done in a steam sterilizer.

On no account should antimony tartrate be kept stored in solution, for it has been ascertained that low forms of fungi develop in it rapidly, with the formation of products of a high degree of toxicity. The same precautions are necessary with the pentavalent compounds of antimony (see p. 149).

Quinine.—The bihydrochloride is the salt most suited for intravenous therapy. This drug is usually sold in ampoules, each containing 9 gr. to 1 c.c. of fluid. For intravenous injection it is sufficient to dilute still further with 9 c.c. of sterile distilled water. The injection should be made slowly, and great care taken not to damage the vessel-wall, otherwise venous thrombosis may result.

Novarsenobillon, "914" (dioxy - diamino - arseno - benzene - monomethyl-sulphoxylate of soda), sold as neosalvarsan, neokharsivan, etc., and other preparations of salvarsan are usually given in doses of 0.3–0.9 grm.

The powder is very soluble, and may be easily dissolved in the sterile capsules in which these preparations are sold. The top of the glass capsule should be filed off, and 4 or 5 c.c. of sterile warm distilled water run in; extra heat is often necessary in order thoroughly to dissolve the powder. The solution should be drawn into the barrel of the syringe and injected, as in the case of tartar emetic, the same precautions being taken.

"Bayer 205" (*Germanin*) is a white soluble powder forming a faint pink solution; 1 grm. is dissolved in 10 c.c. of distilled water. This drug appears to be less irritating to the tissues than the others described.

INTRAMUSCULAR INJECTIONS

Quinine is the drug most usually employed for intramuscular injection.

The site selected is of great importance. Usually the buttock is preferred, and a spot on a horizontal level with the apex of the great trochanter chosen. A 2-c.c. Record syringe is necessary, provided with a sterile needle (Fig. 182).

The bihydrochloride salt of quinine is put up for this purpose in ampoules containing 9 gr. to the c.c. of solution. It does not appear to be desirable to add more solvent, as this might increase the necrotic effect of the solution (p. 81). After preliminary and thorough sterilization of the skin, the needle should be plunged into the substance of the gluteus maximus, care being taken that it does not impinge on the bone.

Salvarsan and derivatives.—The injection should be made above the great trochanter, three finger-breadths below the ilium.

For the more soluble preparations such as sulphoxyvarsan (sulphostab) now on the market, it suffices to dissolve the drug in distilled water, and the injection can be made into the deeper subcutaneous tissues.

INTRAVENOUS INJECTION OF NORMAL OR HYPERTONIC SALINES

For this purpose the apparatus shown in Fig. 184 is necessary; it consists of a graduated glass funnel, and rubber tubing 2 ft. or more in length, provided with a glass junction or window. To the end of the rubber is affixed an intravenous needle, of which a useful pattern is shown in Fig. 184. The lower end of the rubber tubing is provided with a clip by which the flow of fluid through the tube may be carefully regulated by means of pressure between the finger and thumb. The whole apparatus should be sterilized by boiling.

When filling the funnel, care must be exercised to exclude air from it as well as from the rubber tubing. To do this successfully the clips should be released and fluid allowed to flow freely through the rubber tubing, the end of which should be elevated and depressed when any contained air-bubbles can be detected through the glass "window."

When giving an intravenous normal or hypertonic saline the temperature of the fluid in the funnel should be first ascertained. This should be considerably higher than the body-temperature; to allow for loss of heat during manipulation the temperature in the funnel should be 102° F. When the patient is very collapsed the temperature of the fluid should be higher than when the body-temperature is normal.

To insert the needle into the vein, it is necessary to congest the arm, as described on p. 664, by means of a rubber tourniquet. The clip being pressed down, the needle should be inserted boldly and in an upward direction into the prominent median-basilic vein; on releasing the clip, one can easily ascertain whether the vein has been entered, for, if it has not, the saline fluid will distend the surrounding skin.

In a collapsed case, as in cholera, about 4 oz. (115 c.c.) should be allowed to flow in per minute, but when the pulse is restored to a good volume the rate may be slowed down.

It is sometimes advantageous to add 5-per-cent. glucose to the solution.

Various types of needles for intravenous injection are in use. Some are provided with a flange to enable them to ride comfortably over the skin, but, as a general rule, the simpler the construction the easier they are to manage.

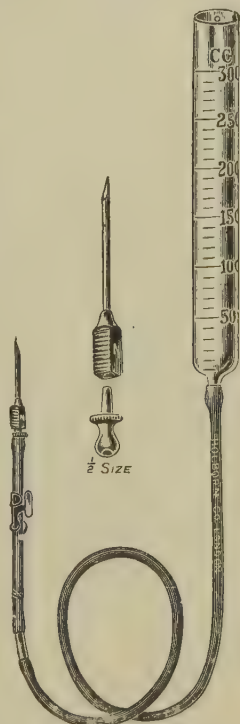


Fig. 184.—Apparatus for intravenous injection, with regulating clip on tube, and special form of intravenous needle.

INTRAVENOUS TRANSFUSION OF BLOOD

The indications for blood transfusion may be stated to be (a) *surgical*, before or after serious operation where there has been much loss of blood, e.g. splenectomy, and (b) *medical*, any severe secondary anæmia, e.g. sprue, blackwater fever, pernicious anæmia and acholuric jaundice.

The donor.—The donor should be between the ages of 20 and 40 years, in good health and have suitable and prominent veins. There should be no history of syphilis, and the Wassermann reaction should be negative, while a recent history of malaria must be excluded. His red blood-corpuscles must not be agglutinated by the recipient's serum; to ensure that this last condition is fulfilled, a direct test should always be carried out prior to transfusion, but, in cases of great urgency, it is permissible to use a donor who is known to belong to the same blood group as the recipient, or belongs to Group IV (universal donor).

The direct test.—The donor should have eaten a good meal about two hours before being bled. About 2 c.c. of the recipient's blood should be drawn and allowed to coagulate. The serum should be pipetted off and a drop placed at one end of a slide; at the other, a small drop of sodium citrate solution (3·8-per-cent.). The donor's finger should be pricked and a small drop of his blood mingled with the citrate. This citrated blood drop is now mixed with the recipient's serum, the slide held over a white background and gently rocked. Should agglutination occur, it will be visible within a few minutes, and if this is the case the blood of the donor is unsuitable. This test is so simple that it should never be omitted.

Technique of transfusion.—A method of giving citrated blood will be described. Methods for transfusing fresh blood direct are considered too uncertain to be of any practical use.

Apparatus.—Two beakers, or Florence flasks, either graduated or marked at the level of 330 c.c. (80–250) are required, each holding about 500 c.c. Needles of short bevel with uniform bores, but of different sizes should be provided, also a tube and glass funnel with suitable rubber connection and needle for giving blood to the recipient (Fig. 184). A glass window should be provided near the needle, so that a view of the contents of the tube may be obtained. Some form of tourniquet is necessary; by far the best is the armlet of a blood-pressure apparatus. A sterile solution of sodium citrate of 3·8-per-cent. strength as being isotonic with the blood, is required.

Method.—The apparatus is tested and sterilized immediately before use. 80 c.c. of citrate solution are placed in each flask. The tourniquet is applied so to congest the donor's arm, by a pressure slightly less than that of the blood-pressure—about 80 mm. of mercury. The skin is cleansed with spirit and iodine over a suitable vein and the largest needle convenient for insertion selected. The skin is steadied and an intravenous needle inserted while an assistant holds one of the flasks to receive the blood. If the needle is held steady, only the first drops of blood are lost. While the blood is running the flask is gently rotated so as to ensure proper mingling of the blood with the citrate solution. When the flask is filled up to the 330 c.c. mark, a second flask is substituted and filled in a similar manner. The armlet is then loosened, the needle withdrawn and a dressing applied. The donor should rest for an hour or so after being bled and allowed to do no work for the rest of the day.

Each flask now contains 80 c.c. of citrate solution mixed with 250 c.c.

of blood and there should be no clotting. These proportions allow an ample margin of citration, so that if it is desired to give more than 500 c.c. of blood, another 100 c.c. can be safely run into each flask. Experience has proved, however, that 500 c.c. is a fair average transfusion. The use of two flasks minimizes the risk of losing all the blood through clotting or other accident. If the transfusion is being completed at once, the flasks should be kept in basins of hot water during filling and for some time subsequently in order to keep their contents at about 105° F., at which temperature the blood will not be injured, and in order to counterbalance the heat lost during the passage through the funnel and rubber tubing.

The armlet is now applied to the recipient's arm after the skin has been prepared. Hot sterile saline is run through the funnel and tube and a small quantity of the citrated blood poured in. Air-bubbles should be expelled and the needle inserted into the recipient's vein, the armlet loosened and the blood allowed to flow slowly. When the recipient's vein is not apparent and doubt is entertained whether it is entered in the proper manner, the shaft of the needle should be inserted into the vein first and the flow of blood observed before connecting up in the manner shown in Fig. 184. At least twenty minutes should be occupied in running in the proper amount, care being exercised throughout to keep the blood at the correct temperature. Difficulty frequently lies in the collapsed and contracted condition of the recipient's veins. By making the armlet tight enough to completely arrest the circulation for about ten minutes, the collected carbon dioxide will cause a local vaso-motor relaxation so that, if the pressure of the armlet be now reduced to the level of that of the diastolic pressure of the recipient, maximum dilatation of the veins will occur. It is for this purpose that a blood-pressure apparatus is preferable to a tourniquet, though with attention to the pulse the latter can be made to serve. Upon the degree of care with which the recipient's veins are dilated and rendered tense, often the success of the transfusion depends.

Evidence of danger.—Evidence that the injection is unsuitable is constituted by the following signs: lumbar pain, fullness in the head, "pins and needles," præcordial oppression, cyanosis, laboured respirations or slow pulse. Any such signs enjoin cessation of the injection at least for a short period. Later, evidence of incompatibility may be shown by rigors, urticarial eruptions or hæmoglobinuria.

APPENDIX

Section A.—MEDICAL ZOOLOGY

I. INTRODUCTORY

THE subject of medical zoology involves the study of all those animals which are either directly or indirectly responsible for human disease. These are the parasitic protozoa, helminths, and arthropoda, which invade or infest the body as direct producers of disease, while there are the various transmitting or intermediate hosts such as insects, crustaceans, molluscs, etc., and animal reservoirs, like rats in plague and big game in trypanosomiasis. In a short account of medical zoology it is impossible fully to deal with all these subjects, but one or two important points should be emphasized.

Transmission.—The transmission of a parasite may be direct or indirect. In direct transmission the parasite, such as the amoeba of dysentery or the round worm, passes directly from one human being to another without the intervention of a transmitting host, e.g. the "contaminative method" of infection. In indirect transmission, the parasite cannot pass directly from man to man without the intervention of some other host, an invertebrate. In such cases the parasite may be conveyed in a purely mechanical manner from one vertebrate to another as it adheres to, or survives in, the mouth-parts of some blood-sucking insect. In "surra" of horses, *Trypanosoma evansi* is thus carried from horse to horse in the proboscis of a tabanid and other biting flies. It is claimed by some that *T. gambiense* may similarly be conveyed from man to man by tsetse-flies, e.g. the "inoculative method" of infection. In these cases, for infection to take place, the interval between the two feeds of the fly is usually not more than a few minutes. In other cases the intervention of a transmitting host is associated with a definite development of the parasite in the invertebrate, so that it is incapable of transmitting the disease till this development has been completed. There exists in these cases a definite biological relationship between the transmitting host or vector and the parasite, the development of which is sometimes associated with a union of gametocytes (*fertilization, syngamy*). Two of the best known examples of this method of transmission are those of the parasites of malaria by mosquitoes and trypanosomes by tsetse-flies. In the case of the former there is a sexual cycle in the mosquito, while no sexual cycle of trypanosomes is known. In the case of several helminths, e.g. *Filaria bancrofti*, the sexual cycle is known, but it occurs in the vertebrate host—man. The host in which the sexual cycle takes place is sometimes known as the *definitive* host. When the development in the transmitting host has been completed after the necessary incubation period, the conveyance of the parasite to the vertebrate host takes place in one of several ways. It may be directly inoculated during the biting act as in malaria and trypano-

somiasis (inoculative method of infection); the parasite may escape through a rupture in the proboscis region on to the skin and then penetrate, as in filaria; or it may be deposited on the skin in the dejecta of the intermediate host and be either scratched into the skin or conveyed to the mouth on the fingers, etc., as is probably the case with *Trypanosoma cruzi*.

Nomenclature.—Students are often confused by what appear to them to be constant and unnecessary changes in the names of parasites and their hosts. The international rules of nomenclature lay down certain laws which, if adhered to, will eventually stabilize the nomenclature and do away with any confusion such as exists at present.

According to the *law of priority*, which is all-important, the valid name of a genus or species can only be that name under which it was first designated, provided that the name was published and was accompanied by a definition or a description. As an example of what this law is meant to imply, the human blood-fluke originally described by Bilharz as *Distomum hæmatobium* may be quoted. On account of the differentiation of the sexes, Weinland separated the genus *Schistosoma* from *Distomum* in 1858, and Cobbold named it *Bilharzia* in 1859; but the latter must be rejected under this law, and the valid name of the parasite accordingly becomes *Schistosoma hæmatobium* (Bilharz, 1852).

The nomenclature of the yellow-fever mosquito, formerly known as *Stegomyia fasciata*, has had to be entirely recast in compliance with this law. The genus *Stegomyia* was originally created by Theobald in 1901, but, in the course of the revision of the genera of mosquitoes which has recently taken place, most authorities consider that *Stegomyia* is not sufficiently demarcated to hold generic rank, but should be included in the recently reconstructed genus *Aedes*.

The specific name *fasciata* is adopted from the description of *Culex fasciatus* Fabricius, 1805, but the species was independently renamed *calopus* by Meigen in 1818. Objections being raised to *fasciatus* as having been pre-occupied, many people adopted the latter specific name, and for some time the mosquito has been named, especially in America, *Stegomyia calopus*; but further research has revealed the fact that this species was described as *Culex argenteus* by the Abbé Poiret in 1787—hence the proper scientific designation has become *Aedes (Stegomyia) argenteus* (Poiret, 1787), Dyar and Knab, 1917. This subject is still more involved since many authorities consider that this insect was named *ægypti* by Linnæus in 1762.

II. MEDICAL PROTOZOOLOGY

Structure of the protozoan cell.—Like the cells of Metazoa, the protozoan cell consists typically of cytoplasm and nucleus. There are various theories as to the minute structure of cytoplasm; according to one view it consists of an emulsion of two liquids of different densities. On fixation and staining, the more liquid part appears as spaces in a network represented by the denser. In addition there are various minute granules distributed in the meshes of the network. The nucleus consists of a nuclear membrane containing a liquid (karyolymph), traversed by a network of fibrils. (Fig. 185.) Distributed in the nuclear membrane and on the fibrils, are granules of chromatin, while a central larger body, the *karyosome*, is frequently present. A *centro-*

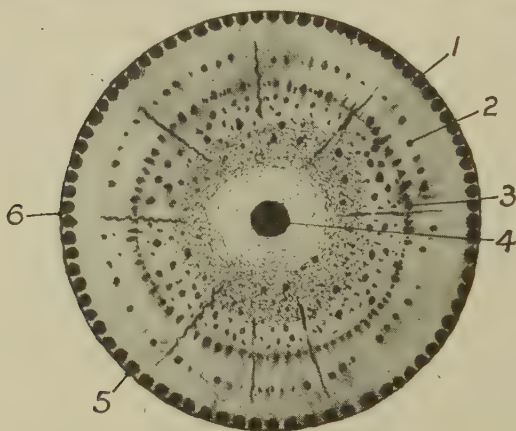


Fig. 185.—Diagram of protozoan nucleus.

- 1, Linin thread; 2, nuclear sap; 3, intermediary chromatin; 4, karyosome (plastin) impregnated with chromatin and linin; 5, achromatic nuclear membrane; 6, nuclear chromatin.

some may be present in the cytoplasm outside the nucleus, or, as some maintain, within the karyosome. In some Protozoa, such as trypanosomes and allied flagellates, there occurs in the cytoplasm in addition to the nucleus, a composite body the *kinetoplast*, composed of a minute *blepharoplast* and a deeply-staining *parabasal* body. The former gives rise to the *axoneme* or axial filament of the *flagellum*. When a protozoon divides, there is first division of the nucleus, followed by division of the cytoplasm (binary fission), or the nucleus may divide repeatedly till numbers are present, after which the cytoplasm segments into a number of portions each with a single nucleus (*schizogony*). In flagellates with a *kinetoplast*, division is initiated by division of the *blepharoplast* and *parabasal*. This is followed by division of the nucleus and cytoplasm in the usual way.

In many Protozoa such as *Entamoeba histolytica*, the cytoplasm is differ-

entiated into a hyaline tough ectoplasm and a more liquid granular endoplasm. The ectoplasm is usually covered by a thin membrane or pellicle. In the Ciliata the ectoplasm is differentiated into a complicated, more or less rigid periplast. In the Sarcodina there are no special organs of locomotion, but extensions of cytoplasm known as *pseudopodia* are formed temporarily. By means of these the organism is able not only to move about but also to ingest solid food. It may even ingest other protozoa in the free and encysted state.

Protozoa may be provided with *organelles*, or minute organs, such as the flagella of *Chilomastix* and *Trichomonas*, which perform lashing movements and thus assist in locomotion. The *flagellum* itself consists of two elements, the central fibre or *axoneme*, and a sheath of cytoplasm; that part of the axoneme between the blepharoplast and the surface of the body is termed the *rhizoplast*.

In the Infusoria, *cilia* are present and richly clothe the ectosarc of the organism, as in *Balantidium coli*. Some genera are provided with a minute oral cavity, or *cytostome*, through which food particles are ingested; this mouth is present in *Trichomonas* and in *Balantidium*. Excretion is assisted by *contractile vacuoles* which are present in free-living Protozoa, but are usually absent in the parasitic form. Food vacuoles in which digestion occurs develop around food particles, and are not usually constant in position.

Multiplication or division of the protozoan cell.—Multiplication may take place in three different ways: (1) *Binary fission*, that is, division of an individual into two equal parts, e.g. *Entamoeba*. (2) *Multiple division*, e.g. schizogony, as in *Plasmodium*, *Hæmoproteus* and coccidia. (3) *Division by budding*, as in *Babesia*.

Two forms of chromatic substance are recognized by some modern authorities—generative and vegetative. The protozoan nucleus contains both forms, while the nucleus of the metazoan somatic cell contains the latter.

The first stages of division take place in the nucleus itself. This may divide in three ways—direct division, or *amitosis*; indirect division with formation of chromosomes, *mitosis* (*karyokinesis*); reduction division, or *meiosis*, by which the number of chromosomes in each of two conjugating gametes is reduced to half, so that, after conjugation, the zygote contains the original number.

The Protozoa are generally divided into four main classes.

CLASS I.—SARCODINA

Protozoa, commonly known as amœbæ, in which the protoplasmic body, having no limiting envelope in the form of a more or less rigid cortical layer, tends to assume a spherical shape when passive, or an irregular, ever-changing shape when in motion. Organs serving for locomotion and capture of food are known as *pseudopodia*. A skeleton or shell may be present. Encysted resistant forms frequently occur. Division into two is the usual method of multiplication.

EXAMPLES : *Entamoeba*, *Endolimax*, *Iodamoeba*.

CLASS II.—MASTIGOPHORA

Protozoa, commonly known as flagellates, in which the organs of locomotion are *flagella*, that is to say, long protoplasmic filaments capable of performing lashing movements.

EXAMPLES : *Trichomonas*, *Giardia*, *Trypanosoma*, *Leishmania*.

CLASS III.—SPOROZOA

Protozoa occurring as intracellular parasites in the blood or tissues. They possess, as a rule, no definite external organs for locomotion or for ingestion of food. The typical reproduction takes place by multiple fission (schizogony) whereby numerous merozoites are produced. When a sexual process occurs, this is followed by the formation of sporozoites. This class includes, amongst others, the orders Coccidia and Hæmosporidia.

EXAMPLES: *Eimeria*, *Plasmodium*, *Gregarina*.

CLASS IV.—INFUSORIA

Protozoa in which small filaments called *cilia* serve as organs of locomotion; these cilia are distinguished from flagella by their much smaller size and in being present in great numbers, sometimes forming a fine covering over the whole of the body. The body protoplasm is always corticate.

EXAMPLE: *Balantidium*.

CLASS I.—SARCODINA

Entamœba histolytica Schaudinn, 1903 (syn. *Endamœba dysentericæ*) (Fig. 186), the pathogenic amœba of man, has been considered in some detail above (p. 404), but a short summary may be given here. These amœbæ vary very much in size. As a rule they measure 20–30 μ in diameter. When active they eject characteristic hyaline pseudopodia. The protoplasm is divisible into two zones—an outer clear ectoplasm and a granular endoplasm. The nucleus, which is generally invisible in the living state, has a characteristic structure with small central karyosome, as is shown in the accompanying figure (Fig. 186, 1). Vacuoles are not present in healthy living individuals, though they may appear in the protoplasm immediately before death. The large active entamœbæ live in the intestinal wall at the bases of the lesions they give rise to, and there undergo binary fission. They ingest red blood-corpuscles, leucocytes, and other portions of the tissues in which they live; this habit serves as a distinguishing feature between *E. histolytica* and the non-pathogenic amœbæ. On cessation of a vegetative life they pass on to encystment, first becoming precystic forms.

The *precystic* forms of *E. histolytica* are probably developed from larger amœbæ by fission and by frequent division small daughter-amœbæ are produced. A shortage of food probably provides the stimulus which leads to encystment. Precystic amœbæ are sluggish and their cytoplasm is devoid of food vacuoles. On account of their small size they were formerly known as *E. minuta*. According to the particular race they vary in size from 5 to 20 μ .

Cysts.—According to Wenyon and O'Connor, Dobell and Jepps, there are different races of *E. histolytica*, distinguishable by the size of their cysts (Fig. 186, 2-5). The smallest measure 7–9 μ or less in average diameter, the largest about 15–20 μ . The mature cyst is quadrinucleate, and very commonly contains within its cytoplasm refractile *chromatoid bodies*; a *glycogen* mass is also usually present and becomes brown in colour upon the addition of iodine solution. The nuclei within the cyst retain the characters of those of the vegetative form.

According to Yorke, mature cysts are unable to undergo any further development in the intestine in which they are produced and under normal circumstances do not hatch there, though Sellards and Theiler have been able to produce acute infection of kittens by intrarectal injection of cysts.

Development of *E. histolytica* from the precystic form to the fully-mature quadrinucleate cyst proceeds in the lumen of the bowel. The whole process only occupies a few hours and the quadrinucleate cyst can only survive in the bowel about two days. Fluid is necessary for excystation. From a fully-mature quadrinucleate cyst one quadrinucleate amoeba emerges which subsequently divides into four uninucleate individuals.

Artificial culture.—After many unsuccessful attempts, the cultivation of *E. histolytica* on artificial media has been effected by Boeck and Drbohlav in 1925. They use solid blood-agar or solidified egg-slopes covered with Locke's solution (see p. 865). The addition of a pinch of finely-powdered

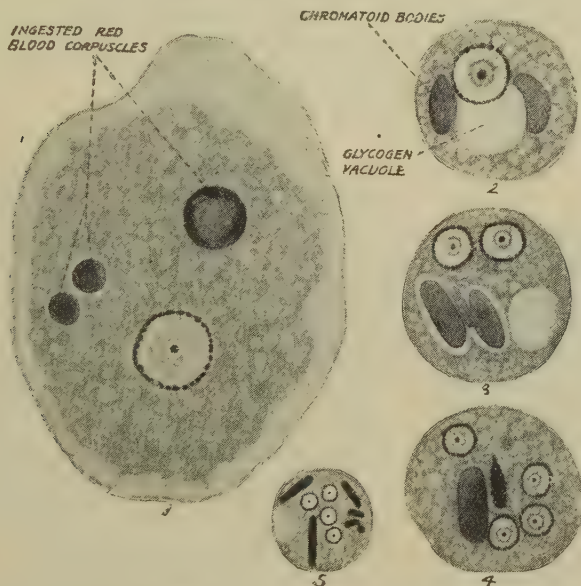


Fig. 186.—*Entamoeba histolytica*. $\times 2,500$. (After Dobell.)

1, Active amoeboid form with ingested red blood-corpuscles. 2, Uninucleate cyst. 3, Binucleate cyst. 4, Quadrinucleate cyst. 5, Quadrinucleate cyst, small race, 6.6μ in diameter.

rice starch (collar starch) to each tube of the medium greatly aids the growth of the amoebæ which ingest the granules with avidity. The cultures are kept at 37°C . and must be reinoculated every two to three days. Subcultures which have been maintained for one-hundred-and-fifty generations are still capable of producing amœbic dysentery when injected into kittens. In blood-agar cultures, and similarly in egg cultures, if the starch is withheld from a subsequent subculture and fresh blood is introduced, the entamoebæ will ingest red blood-corpuscles. Cultures may be obtained either from the active vegetative forms or from the cysts; in the latter case even after the faeces have been passed for as long as nine days.

As *Entamoeba dispar*, Brumpt recognizes a "physiological species" morphologically indistinguishable from *E. histolytica* but not capable of engulfing red blood-corpuscles. It produces four nucleated cysts, is non-pathogenic

to man and pathogenic only in a mild degree when injected into cats. It apparently lives in the fæces and does not invade the bowel-wall. It is not regarded as a distinct species by most observers.

Entamoeba coli (Grassi, 1879) (Fig. 187).—*E. coli* is on an average larger than *E. histolytica*, but is subject to great variation in size. The size of the active stage of the organism may vary from 10 to 40 μ ; as a rule it is 20–30 μ in diameter. Its movements are, as a rule, more sluggish than those of *E. histolytica*; the sudden extrusion of pseudopodia is never seen. The cytoplasm is bulky and granular, and is usually charged with food vacuoles containing various objects such as bacteria, and even cysts of other protozoa like *E. histolytica*, *Giardia*, *Isospora*, but never with red blood-corpuscles or tissue elements. There is not the differentiation of the cytoplasm into ectoplasm and endoplasm as occurs in *E. histolytica*. *E. coli*, in fact, leads a commensal existence in the fæces of the large intestine and does not live



Fig. 187.—*Entamoeba coli*.
× 2,500.
(After Dobell.)

- 1, Cyst with eight nuclei. 2,
Active amoeboid stage with
ingested food material.

in the bowel-wall. It is of a greyish colour and this, with the large number of food vacuoles containing bacteria and other objects, serves to distinguish it from *E. histolytica*. Sometimes the vacuoles resemble fissures.

Compared with that of *E. histolytica* the nucleus is large, coarse and easily visible in the unstained state. The chromatin granules on the nuclear membrane are relatively coarse, while other granules occur on the linin network. The karyosome which is larger than that of the nucleus of *E. histolytica* is eccentric in position and is surrounded by a clear area limited by granules.

Though these nuclear characters are seen in perfectly fresh specimens, as in the case of *E. histolytica*, they are frequently lost in individuals which are in the slightest degree degenerate.

Like other entamoebæ, *E. coli* reproduces by binary fission. Prior to encystation the amoebæ undergo a considerable reduction in size, with the result that the precystic forms can with difficulty be distinguished from those of *E. histolytica*.

Cysts.—The cysts (Fig. 187, 1) exhibit a considerable variation in size, 10–30 μ ; and there is little doubt that, like *E. histolytica*, *E. coli* is a composite species, consisting of a number of races distinguishable by the dimensions of their cysts. The resting nucleus within the cyst bears the same characters as does that of the active form. The single nucleus, which is at first present in the cyst, divides by binary fission into two, four, and eight, the nuclei progressively diminishing in size. The mature cyst is octonucleate, though it must be remembered that immature quadrinucleate cysts occur, and occasionally supernucleated cysts with sixteen nuclei. The cytoplasm of the cyst contains a variable amount of glycogen, which is most abundant in the binucleate form, and may be demonstrated with iodine solution. Chromatoid bodies are not always present, appearing more generally as small granular or rod-like bodies, especially in the binucleate stage. In mature octonucleate cysts they are, as a rule, absent, though when present they are usually in the form of pointed threads or splinters.

The life-history of *E. coli* is similar to that of *E. histolytica*, save that the

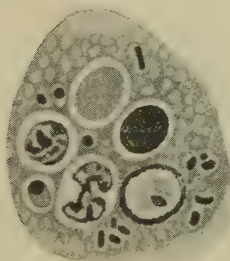


Fig. 188.—*Entamoeba gingivalis*: active amœboid form with eccentric nucleus and ingested bodies. $\times 2,500$. (After Dobell.)

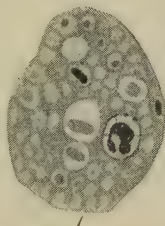


Fig. 189.—*Endolimax nana*. $\times 2,500$ (After Dobell.)

1, Active amœboid form. 2, Quadrinucleate mature cyst



large vegetative forms inhabit the fæces, instead of the tissues of the host. Like *E. histolytica*, *E. coli* may be cultivated upon artificial media.

E. coli infections are not affected by emetine.

Incidence of E. coli.—This organism is common in man, both in temperate zones and in the tropics; it is probably more easily found in the fæces of dysenteric cases and is found in about 15 per cent. of normal individuals. Various animals, especially monkeys, harbour species of entamœbæ resembling *E. coli* and *E. histolytica*. Those in the monkey are not improbably identical with those in man.

Entamoeba gingivalis (Gros, 1849) (Fig. 188).—The amœba of the mouth was the first amœba discovered in man. Bass and Johns (1915) considered it to be the cause of pyorrhœa alveolaris, but this has been disproved. It is a small amœba showing great variations in size—from 10 μ to 25 μ in diameter. Endoplasm and ectoplasm are rather sharply differentiated, and the cytoplasm is filled with food vacuoles and peculiar inclusions of a greenish, refractile appearance. The nucleus is spherical and vesicular, varies in diameter from 2.5 μ to 3 μ , and is slightly smaller in proportion to the rest of the organism than is the nucleus of *E. histolytica* or *E. coli*. The

nuclear membrane is very definite and is dotted over with granules of chromatin. Apart from the peculiar greenish refractile bodies, which may be the remains of salivary corpuscles or polymorphonuclear cells. *E. gingivalis* usually contains large numbers of bacteria. The amœba probably reproduces by binary fission, although all the stages have not been observed. It is also probable that this species does not form cysts, though bodies believed to represent this stage have been described.

TABLE SHOWING DIFFERENTIAL CHARACTERS OF THE COMMONER INTESTINAL AMCEBÆ

<i>Entamœba coli.</i>	<i>Entamœba histolytica.</i>	<i>Endolimax nana.</i>
Size: 18-40 μ .	20-30 μ .	6-12 μ .
Morphology: No distinction between endo- and ecto-plasm.	Granular endoplasm; clear ectoplasm.	Granular and rather vacuolated cytoplasm.
Ingests bacteria, other protozoa, etc.	Ingests red cells, tissue cells, etc.	Ingests bacteria and food granules.
Nucleus distinct in fresh specimens. Coarse chromatin granules on nuclear membrane. Eccentric karyosome surrounded by coarse ring.	Nucleus inconspicuous in fresh specimens. Fine chromatin granules on nuclear membrane. Central karyosome surrounded by delicate ring.	Clear nuclear membrane and massive, irregular karyosome.
Sluggish movement with granular pseudopodia.	Active movement with clear, blunt pseudopodia.	Sluggish movement with clear pseudopodia.
Multiplication: By binary fission in fæces. Encystment and formation of 1, 2, 4, and 8 nucleated spherical cysts, 10-30 μ in diameter.	By binary fission in intestinal wall. Encystment and formation of 1, 2, and 4 nucleated spherical cysts, 7-15 μ in diameter.	By binary fission in fæces. Encystment and formation of 1, 2, and 4 nucleated oval cysts 8-10 μ in length by 7-8 μ in breadth.
Chromatoid bodies typically not present in the mature cyst.	Chromatoid bodies especially present in the mature cyst.	Chromatoid bodies not present in the cyst.

Endolimax nana (Wenyon and O'Connor, 1917) (Fig. 189).—This species is of importance in so far that its quadrinucleate cysts, which are sometimes spherical, resemble the smaller cysts of *Entamœba histolytica*. It is commonly present in normal fæces, and has been recorded in some 33 per cent. of dysenteric and diarrhœic stools. It is a small amœba, 6-12 μ in diameter, with characteristic vesicular nucleus and a large and irregularly-shaped karyosome. It probably inhabits the small intestine, living upon the intestinal contents. The cysts (Fig. 189, 2) are characteristic structures of the same size as the active form, and contain, when mature, four nuclei, a few visible refractile granules, but no vacuoles or chromatoid bodies. Glycogen

cannot always be demonstrated in the cysts, though it is most commonly found in the binucleate forms. The cysts vary in shape from a typical oval to a sphere; very small ones are $6\ \mu$ in diameter. Occasionally they contain peculiar inclusions resembling long and filamentous rods or granules, and are then liable to be mistaken for cysts of *Giardia intestinalis*.

Like *Entamoeba coli*, *Endolimax nana* is non-pathogenic and injections with it are not amenable to emetine treatment.

E. nana may be cultured to a limited degree on Boeck's and Drbohlav's medium.

Iodamoeba bütschlii (Prowazek, 1912) (Fig. 190).—The cysts formerly described as "iodine cysts" or "I. cysts" in human faeces are now definitely known to belong to this amoeba. A similar organism has been described from the dejecta of monkeys and pigs. *I. bütschlii* is a small amoeba, intermediate in size between *E. coli* and *E. nana*. It measures from 9 to $20\ \mu$ in diameter, but very small individuals $5\ \mu$ in size have been recognized.

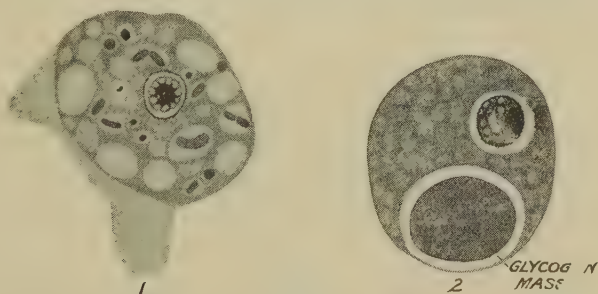


Fig. 190.—*Iodamoeba bütschlii*. $\times 2,500$. (After Dobell.)

1, Active amoeboid form with ingested micro-organisms. 2, Mature cyst, "iodine cyst," containing large glycogen mass.

In form and habit it is very like a small specimen of *E. coli*. The cytoplasm is filled with food vacuoles containing bacteria and other food particles. The nucleus, which is often quite invisible in organisms containing much food, has a diameter of about one-fifth to one-fourth of that of the whole organism; it is vesicular, and has a moderate-sized central, intensely-staining karyosome, $2\text{--}3.5\ \mu$ in diameter. The nuclear membrane is well developed. Between it and the karyosome is a clear zone occupied by a layer of small granules. *I. bütschlii* feeds chiefly upon the micro-organisms of the large intestine, which it inhabits. Multiplication of this amoeba is by binary fission.

The cysts are remarkable uninucleated structures, very frequently irregular in outline, but typically spherical or oval, and measuring $9\text{--}12\ \mu$ in diameter. Owing to the irregularities in their shape, they are often difficult to measure with certainty, but $6\text{--}16\ \mu$ may be taken as extremes of the largest diameter. They contain numerous refractile granules formed of a substance called *volutin*, and, almost invariably, a comparatively large and dense glycogen mass, most readily seen when the cysts are suspended in iodine solution. Sometimes two or even three separate masses may be found in the same cyst. The cyst nucleus, eccentrically placed, is of a comparatively large size, $2\text{--}2.5\ \mu$. The karyosome, which is centrally situated in the nuclei of active precystic amoebae, gradually passes during encystment to the periphery and becomes a large compact mass in contact with the nuclear membrane.

The mature uninculeate cysts of this amœba, save for the disappearance of the contained glycogen, undergo no further changes outside the human body.

I. bütschlii occurs in about 5 per cent. of fæces, most commonly in those who have been in the tropics, and not infrequently in association with *E. histolytica*.

Infections showing both the active forms and the cysts of *I. bütschlii* are extremely amenable to emetine and emetine-bismuthous iodide. How this drug acts it is difficult to say, for it is without effect upon *E. coli* and *E. nana* infections.

Dientamœba fragilis Jepps and Dobell, 1918 (Fig. 191), is a very small amœba, 3.5–12 μ in diameter, its usual size being 8–9 μ . It lives in the large intestine. It is actively motile, with marked differentiation between ecto- and endo-plasm. The pseudopodia are lobed and indented. It is a rare amœba, and very few cases of infection with it have so far been described. Each individual is typically binucleate. In size the nucleus ranges

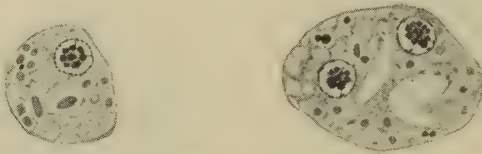


Fig. 191.—*Dientamœba fragilis*, uninucleate and binucleate forms.
× 2,500. (After Dobell.)

from 0.8 μ to 2.3 μ ; it is spherical, the karyosome being large and composed of a number of granules embedded in a plastin matrix. After leaving the body the amœba quickly degenerates. It would appear to live exclusively upon bacteria and other small micro-organisms. It is doubtful if cysts have been seen.

"Amœba limax" is a term applied to many different free-living amœbæ occurring in water and earth. The cysts possess a hard and refractile wall. These forms are of importance to the tropical pathologist as the cyst may be swallowed with food, and after passage through the intestine appear in the stools of dysenterics and normal individuals and give rise to cultures of amœbæ in stale fæces or on the surface of Musgrave and Clegg's medium. Free-living amœbæ, which pass through the intestine in the encysted state in this manner, are known as coprozoic amœbæ. They must not be confused with the smaller parasitic forms like *Endolimax nana* which, however, quickly die and degenerate in stale fæces.

Parasitism.—Most of the intestinal amœbæ of man are liable to be invaded by a fungus known as *Sphæritia*; this consists of small spherical masses of a coccus-like body which is refractile in a living condition and occurs within vacuoles of the cytoplasm.

CLASS II.—MASTIGOPHORA

The Mastigophora are divided into several subclasses, of which only one, that of the *Zoomastigina* or *Flagellata*, demands our attention, and within this group we shall consider only the two orders *Protomonadina* and *Poly-mastigina*.

ORDER i.—PROTOMONADINA

HÆMOFLAGELLATA (BLOOD FLAGELLATES)

The genera representing the more important types are : (1) *Trypanosoma* (2) *Leishmania*, (3) *Leptomonas*, (4) *Crithidia*, and (5) *Herpetomonas*. The two former occur in the blood or tissues of man and are pathogenic organisms ; the three latter do not occur in man, but it is necessary to consider their structure in relation to certain stages in the development of the former.

1. *Trypanosoma*

The structure of the trypanosome body is of a uniform type, though subject to variation in minor details. The body is slender ; the anterior¹ end tapers gradually to a fine point, while the posterior generally terminates more bluntly. (Fig. 192.) The general shape of the body is, that of a curved, flattened blade.

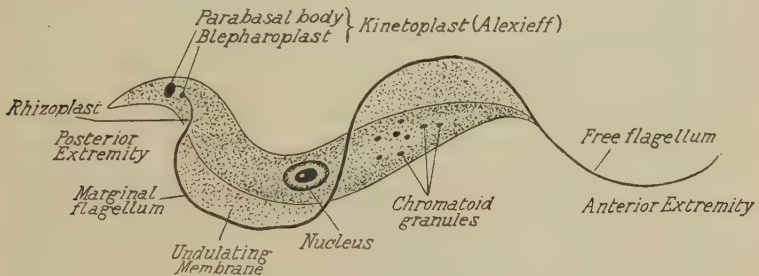


Fig. 192.—Schema of *Trypanosoma*. (After Dobell.)

The nucleus (triphonucleus) is situated centrally ; the kinetoplast is usually placed posteriorly to the nucleus, but is sometimes closely approximated to it. Certain exceptions to this rule are known, namely, *T. rhodesiense* (p. 684), *T. brucei* and some multiplicative forms of *T. lewisi*. The axoneme, the axial filament of the flagellum, arises from a blepharoplast, and passes forwards along the margin of the undulating membrane ; in some cases it may end with the undulating membrane at the anterior extremity of the body ; but more usually it is continued forwards into the flagellum. Trypanosomes in which the axoneme extends beyond the anterior end of the body into the flagellum are said to have a free flagellum.

Trypanosomes multiply by binary fission. The kinetoplast (blepharoplast and parabasal) first divide. This is followed by division of the nucleus and formation of a new flagellum and membrane. The body then divides longitudinally from before backwards.

Trypanosomes occur as blood parasites in all classes of vertebrates. Many wild animals harbour them in their blood. They are very specific to a particular host and are in most cases harmless parasites.

Transmission.—Except in the case of *Trypanosoma equiperdum* which is handed on from horse to horse during coitus, trypanosomes are transmitted from one vertebrate host to another by blood-sucking invertebrates,

¹ The terms "flagellar" and "aflagellar" may be used to designate the extremities of the body, instead of the terms "anterior" and "posterior" respectively, which are here employed strictly with reference to the mode of progression.

usually insects, and in the cases of fish, leeches. In some cases, as for instance *Trypanosoma evansi*, the transmission is a purely mechanical one, a biting fly feeding on an infected animal and within a few minutes, or at most a few hours, biting an uninfected one, and inoculating trypanosomes which have merely remained alive in or on its proboscis. In most cases, however, transmission is associated with a definite developmental cycle in the fly, so that after an infective feed there is an incubation period before the fly becomes infective. Infectivity is always dependent on the final production in the fly of a special type of trypanosome known as the metacyclic trypanosome.

There are two main types of development. In the one the development commences in the stomach, the developing forms spreading forwards to the proboscis and salivary glands, or the development is confined entirely to the proboscis, while in the other the development commences in the stomach, the developing forms passing backwards to the hindgut. The first type of development is referred to as taking place in the *anterior station*, and the second type as in the *posterior station*. In the case of anterior development, the metacyclic infective trypanosomes are inoculated during the biting act, while in the case of the posterior development the metacyclic infective trypanosomes escape in the faeces of the insect and gain entrance to the mouth of the vertebrate and bring about infection in that way.

The pathogenic trypanosomes of Africa are transmitted by species of *Glossina* in which three types of development in the anterior station occur. In the case of *T. gambiense*, *T. rhodesiense* and *T. brucei*, the ingested trypanosomes commence to develop and multiply in the stomach, where finally a long slender type of trypanosome is produced. This form migrates forwards to the proventriculus and thence to the proboscis and salivary glands. In the salivary glands it becomes transformed into crithidial forms which attach themselves to the glandular cells. Finally they are converted into metacyclic trypanosomes which resemble those originally present in the blood. These trypanosomes are inoculated with the saliva when the fly bites. In the case of *T. congolense* there is at first a stomach phase of development, but the long slender trypanosomes pass forwards to the proboscis only, and not to the salivary glands. It is in the proboscis that the crithidial forms and finally the metacyclic trypanosomes are produced. Finally in *T. vivax* there is no stomach phase of development, the trypanosomes developing only in the proboscis where the crithidial forms and metacyclic trypanosomes are evolved.

In all other instances of known transmission of trypanosomes associated with development in intermediate hosts the evolution is in the posterior station. Thus in *T. cruzi*, transmitted by reduviid bugs, such as *Triatoma megista*, the development commences in the stomach and proceeds in the hindgut where numerous crithidial forms are produced. Finally metacyclic trypanosomes are evolved which escape from the intestine of the bug in its faeces. From what is known of the transmission of the rat-trypanosome, *T. lewisi*, by the flea, and the sheep-trypanosome, *T. melophagium*, by the ked, it seems probable that infection of the vertebrate with *T. cruzi* is brought about by the ingestion of the faeces of the bug.

Cultivation.—Trypanosomes can be cultivated in certain blood-media. Those of cold-blooded vertebrates and birds and the non-pathogenic species of mammals such as *T. lewisi*, *T. theileri*, *T. melophagium*, etc., are easily cultivated in N.N.N. medium or some of its modifications. The pathogenic forms like *T. gambiense*, *T. rhodesiense*, *T. brucei*, *T. congolense*, *T. vivax* and *T. evansi*, are very difficult to cultivate in this medium, though in a

primary culture they will change in form and survive for many days. Subculture is difficult to obtain. In more complicated media it is sometimes possible to carry on cultures for many generations. On the other hand, *T. cruzi* resembles the non-pathogenic trypanosomes in being more readily cultivated.

Generally speaking the trypanosomes in cultures tend to develop along the lines of the cycle in the invertebrate. Crithidial forms are produced, and after these have multiplied for some time there again appear trypanosome forms which probably correspond with the metacyclic trypanosomes developed in the invertebrate host.

Trypanosoma gambiense, Dutton, 1902.—This trypanosome never occurs in the blood of man in great numbers. Sometimes it can be more readily found in the fluid obtained by puncture of an enlarged lymphatic

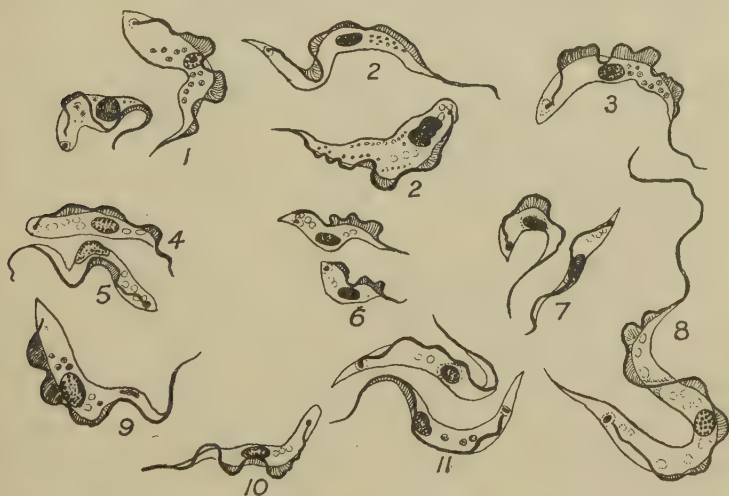


Fig. 193.—Various trypanosomes of man and animals. $\times 1,300$.

(After Wenyon.)

1, *T. gambiense*; 2, *T. rhodesiense* (brucei); 3, *T. evansi*; 4 and 5, *T. uniforme*, *T. vivax*; 6, *T. congolense*; 7, *T. cruzi*; 8, *T. theileri*; 9, *T. equinum*; 10, *T. equiperdum*; 11, *T. lewisi*.

gland, or in the cerebro-spinal fluid. It varies much in length and breadth during different stages of its existence; as a general rule, it measures 18–30 μ in length, by 1–3 μ in breadth (Fig. 193, *r*). Three types are normally recognized—short stumpy forms without free flagellum, long slender forms with free flagellum, and intermediate forms.

The parasite is found, not only in the blood, but in the lymphatic glands, the cerebro-spinal fluid, and the substance of solid organs, especially the brain. Most laboratory and domestic animals can be infected with this trypanosome, but baboons (*Cynocephalus*) and the sooty mangabey monkey (*Cercocebus fuliginosus*) are refractory. *Trypanosoma nigeriense* is considered to be merely a local variety of *T. gambiense*.

Development of T. gambiense in Glossina palpalis.—Trypanosomes are ingested by the glossina and during the first few days of their residence in

the stomach of the fly, multiplication proceeds, trypanosomes of various shapes and sizes being produced, until by the seventh to the tenth day they exhibit a very wide range of form. From the tenth to the twelfth day onwards long slender forms appear in great number, and gradually migrate towards the proventriculus of the fly, in which organ they become the predominant type. The proventricular forms migrate to the salivary glands, where they assume a crithridial shape and attach themselves to the wall of the ducts. (Fig. 196.) Development in the salivary gland proceeds for a period of from two to five days, when there are produced metacyclic trypanosomes, which are the forms infective for man.

Under optimum conditions the complete cycle of development in the tsetse-fly takes at least eighteen days. Moreover, of the total number of flies fed on blood containing trypanosomes, multiplication of the organism takes place in only 8 per cent., and in a still smaller proportion only are metacyclic infective forms produced.

Reservoir-hosts.—In the laboratory most forms of the South African antelope have been experimentally infected from the bites of infective glossinæ, but under natural conditions it is improbable that all forms of antelope act as reservoir-hosts of this trypanosome. The swamp-dwelling forms, particularly "the situtunga," *Limnotragus spekei*, have fallen under suspicion. In addition to these, all domestic animals, even sheep, and dogs, may be naturally infected, but they succumb as a rule so rapidly that they cannot be considered so much a source of danger as are the wild game.

Trypanosoma rhodesiense, Stephens and Fantham, 1910.—In the blood of man *T. rhodesiense* is indistinguishable from *T. gambiense*, the same three types being recognizable; in order to differentiate it, it is necessary to sub-inoculate the strains into laboratory animals, preferably the rat. In this host a change takes place in the position of the nucleus; whereas in *T. gambiense* it is always anterior to the kinetoplast, in *T. rhodesiense* in a varying proportion of the trypanosomes it assumes a position close to the kinetoplast or, in a very few cases, actually posterior to this structure. The proportion of posterior nuclear forms, which are notably shorter than the normal, rarely constitutes more than 5-6 per cent. of the total number of trypanosomes (Fig. 193, 2).

Some authorities regard *T. rhodesiense* as representing the human strain of *T. brucei*, while recently in Uganda the International Commission claims that posterior nuclear forms may occur rarely in *T. gambiense* infections, and that probably *T. rhodesiense* is merely the former trypanosome transmitted through a different species of glossina, or a more virulent race of it.

Geographical distribution.—This trypanosome has a limited geographical distribution, being confined to northern Nyasaland, north-eastern Rhodesia, Portuguese East Africa, and the Southern Sudan, but is thought to be extending its range. Its pathogenicity is greater than that of *T. gambiense*, it is more resistant to treatment, and is more virulent to laboratory animals.

Development in G. morsitans.—As far as is known, the development of *T. rhodesiense* in *G. morsitans* and other tsetse-flies is identical with that of *T. gambiense* in *G. palpalis*. Probably it is this species which is transmitted by *G. swynnertoni* in Mwanza (Tanganyika Territory).

Trypanosoma (Schizotrypanum) *cruzi*, Chagas, 1909. Synonyms, *T. escomeli*.—Occurs in the blood of man in Brazil, Venezuela, and the Argentine, causing a disease known as Chagas' disease. The development of this trypanosome (Fig. 194) differs materially from that of any of the preceding,

by the method of multiplication in the body. When present in the blood-stream it is dimorphic, some forms being broad and others narrow. The posterior end is sharp and wedge-shaped, while the parabasal body is large; individuals measure about $20\ \mu$ in length. (Fig. 193, 7.) This trypanosome was first discovered in the bug by Chagas, and subsequently the infection was found in man.

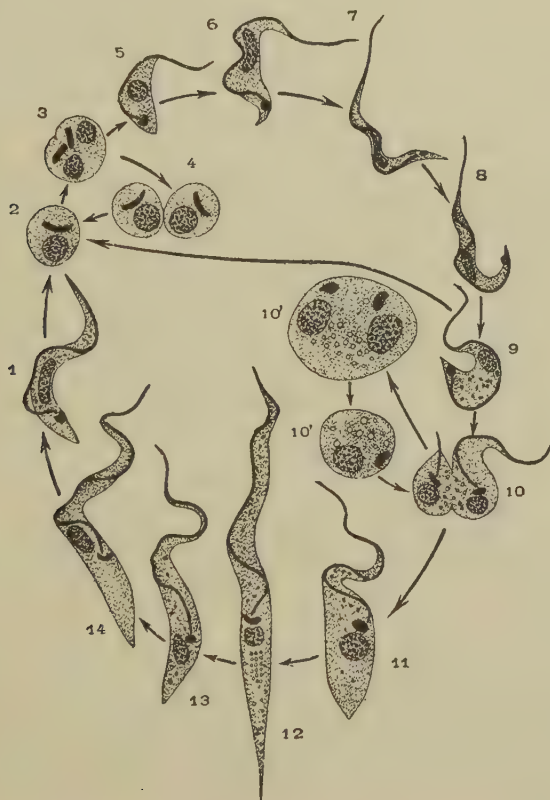


Fig. 194.—Evolutionary cycle of *Trypanosoma cruzi*: 2-9 in man or other vertebrate; 9-14 in *Triatoma* or *Cimex*. $\times 1,500$. (After Brumpt.)

1, Metacyclic trypanosome infecting vertebrate; 2, 3, 4, schizogony in organs; 5-9, transformation of adult trypanosome (9); 10, crithidial form about to divide in small intestine; 10', leishmania forms frequent in the proventriculus; 11-14, progressive transformation of crithidia forms into metacyclic trypanosomes (1) in hindgut.

Certain individual trypanosomes leave the blood-stream and enter the muscles, especially those of the heart, or it may be the cells of the brain or other organs, and there undergo a series of rapid binary fissions during which they assume a leishmania form. Multiplication of these leishmania forms is so rapid that soon a quarter of the tissue is invaded. Four or five days later the leishmania forms become elongated and assume a crithidial form,

and are transformed once more into trypanosomes, which make their way through the tissues and regain the blood-stream.

Trypanosomes are taken up from the blood of man by a Reduviid bug, *Triatoma megista*, in which they undergo an elaborate development; this can occur either in the larval, nymphal, or adult stage of the insect. They pass from the stomach into the small gut and become transformed into crithidial forms, and in this state continue to multiply rapidly. From eight to ten days later the metacyclic or infective trypanosomes make their appearance, and pass out in the fæces of the insect. Inoculation of the parasite into man would seem to take place through the ingestion of fæces or the rubbing of fæcal matter into the wound made by the bug, though some investigators claim to have transmitted the disease through the bite of *Triatoma* (Fig. 194).

Under experimental conditions the parasite can be inoculated into rats, mice, rabbits, guinea-pigs, and monkeys, and can pass through the mucous membrane of the mouth or conjunctiva, which, according to recent work, must have some slight injury or abrasion.

Reservoir-hosts.—Armadillos—*Tatusia novemcincta*, *Dasypus sexcinctus*, and *D. unicinctus*—appear to be natural carriers of infection. The cat has been found naturally infected. Numerous bugs can act as definite hosts. *Triatoma infestans*, *T. sordida*, *T. vitticeps*, *T. dimidiata* var. *maculipennis* are found naturally infected in Brazil; *Rhodnius prolixus* and *Erathyrus cuspidatus* in Venezuela. The bug, *Triatoma protracta*, a species common in California and extending as far north as latitude 41° (Salt Lake City) harbours a flagellate like *T. cruzi*, but the human disease is unknown in this area. Under experimental conditions other species of *Triatoma* of the United States can be easily infected, as well as the cosmopolitan *T. rubrofasciata*; in fact, it is probable that all species of *Triatoma* and allied genera are susceptible. Under laboratory conditions, Brumpt has obtained development of and persistence of the parasite in *Cimex hemiptera* (*rotundatus*), *C. lectularius*, *C. boueti*, and *C. hirudinis*, also the African ticks, *Ornithodoros moubata* and *O. savignyi*.

The multiplicity of the vicarious hosts of *T. cruzi* would certainly indicate that the disease it gives rise to could spread in many countries if all conditions were favourable; the reduviids are so easily infected that it is possible to infect 100 per cent. of them at all stages of their existence; moreover, once infected they remain so for life, they themselves not suffering from the effects of thus being parasitized. It seems probable that the trypanosome is naturally a parasite of armadillos, etc., and that it occasionally becomes inoculated to man.

TRYPANOSOMES OF ANIMALS RESEMBLING THOSE PATHOGENIC TO MAN

Trypanosoma brucei, Plimmer and Bradford, 1899, is morphologically identical with *T. rhodesiense*, and is possibly the same species. It was discovered by Bruce in 1895 in the blood of horses suffering from "nagana," the "fly disease of Africa." The normal hosts are the African antelopes, and probably also buffaloes (Fig. 193, 2).

The development of this trypanosome takes place in various glossinæ, notably *G. morsitans*, *G. tachinoides*, *G. brevipalpis*, and *G. pallidipes*. The developmental cycle in the glossina is similar to that of *T. gambiense*.

This trypanosome causes a fatal disease in all domestic animals in Central Africa, notably horses, mules, and donkeys. The symptoms produced con-

sist of œdema, cachexia, and often blindness. The big game of the "fly belts," although heavily infected, show no symptoms of disease. This parasite produces also a disease called "aino" in camels in Somaliland.

Trypanosoma congolense Broden, 1904. Synonyms, *T. dimorphon*, *T. pecorum*, *T. nanum*. This parasite, the smallest of the pathogenic African trypanosomes, is widely distributed throughout Africa, and is a parasite of horses, mules, cattle, sheep, and pigs, while dogs, cats, and most laboratory animals are susceptible. Its pathogenicity is not of a high order. It is a short trypanosome, measuring 12–14 μ by 1 μ ; the posterior extremity is rounded, and the undulating membrane only slightly developed. There is no flagellum. Development takes place in *Glossina palpalis*, *G. morsitans*, *G. tachinoides*, and *G. longipalpis*.

The trypanosomes multiply in the stomach developing into long slender forms which migrate to the proboscis where they are converted into crithidial forms and, finally, into metacyclic infective trypanosomes (Fig. 193, 6).

Trypanosoma simiæ Bruce, 1912, morphologically resembles *T. congolense*, save that it is distinctly larger. It is remarkably virulent to monkeys and to the pig, but rats and guinea-pigs are refractory. The transmission of *T. simiæ* is by *Glossina morsitans*. Development commences in the stomach and finally the labial cavity is infected. Crithidial forms are evolved which invade the *hypopharynx* and become metacyclic trypanosomes.

Trypanosoma vivax Ziemann, 1905. Synonyms, *T. cazalboui*, *T. bovis*, *T. capræ*, *T. uniforme*.—This is a parasite of sheep, cattle, and goats on the Upper Niger and in the Cameroons, Congo Free State, Uganda, and Rhodesia, while identical organisms have been found in one human case in West Africa by Macfie. The disease it produces in these animals is known as "souma." The posterior extremity is rounded, the nucleus is oval, the kinetoplast being situated at the extreme posterior end. The undulating membrane exhibits no marked folding; the flagellum is free posteriorly. (Fig. 193, 4, 5.) As its name implies, the trypanosome is exceedingly active in the blood.

Development takes place in various glossinæ, *G. palpalis*, *G. tachinoides*, *G. longipalpis*, and *G. morsitans*, especially the first-named species, and is confined to the proboscis; the insects become infective after a period of six to seven days. In the proboscis the trypanosomes rapidly change into crithidial forms which attach themselves to the walls of the labrum, resulting in the production of clusters of flagellates which eventually develop into small, actively motile metacyclic trypanosomes.

This parasite occurs as a natural infection in the situtunga (*Limnotragus spekei*) and other antelopes.

Trypanosoma evansi Steel, 1885.—This parasite, discovered in 1880, in India, causes a disease in horses called "surra"; it also affects camels, elephants, buffaloes, and dogs. As a rule, the disease in cattle is of a milder type. Under experimental conditions it can be transmitted to most laboratory animals. It is morphologically similar to *T. equinum* and *T. equiperdum* (the former of these two has no distinguishable parabasal body). Various species of *Tabanus* and other biting flies transmit the parasite in a mechanical manner (Fig. 193, 3).

In South America a variety of this parasite, *T. hippicum*, produces a disease called "murrina" in mules.

A disease of dromedaries in the Sahara, known as "mbori" and transmitted by *Tabanus ditaniatus*, is also due to a variety of this parasite.

Trypanosoma equinum Voges, 1901, can be distinguished morphologically from trypanosomes of the same type by the absence of the parabasal body. It causes a disease known as *mal de caderas* in Central and South America, and occurs as a natural infection in the capibara (*Hydrochaeris capibara*) which possibly acts as a reservoir-host. Nothing positive is known about its transmission (Fig. 193, 9).

Trypanosoma equiperdum Doflein, 1901, synonym *T. rougeti*, closely resembles *T. evansi*. It is transmitted through coitus, and produces a disease of stallions and mares known as dourine or *mal du coït* in Europe, Africa, and South America. Symptoms consist of an edematous inflammation of the penis and vagina, and a skin eruption in the form of plaques. The organisms occur but scantily in the peripheral blood, and are mainly found in the genital and skin lesions (Fig. 193, 10).

Trypanosoma theileri Laveran, 1902. This trypanosome is twice the size of any of the preceding species, being 60–70 μ in length by 5 μ in breadth. It is found in cattle in many parts of the world, and is thought to be transmitted by species of *Tabanus*. *T. theileri* has frequently been demonstrated in the blood of cattle by the cultural method, when direct blood-examination has been negative. This parasite is non-pathogenic.

Trypanosoma melophagium Flu, 1908.—This parasite, which occurs as an extremely scanty infection in the blood of domestic sheep, is large—47 μ in length—with a short, free flagellum. The kinetoplast is situated close to the trophonucleus. Though it is rarely found in blood-films, artificial cultures are comparatively easily obtained, and must be kept at a temperature above 30° C.

The sheep-ked (*Melophagus ovinus*) is the transmitting host; the trypanosomes become converted into crithidia, which are very numerous in the hindgut, and which were previously regarded as a parasite peculiar to this insect, *Crithidia melophagia*. The crithidial form soon becomes transformed into small infective trypanosomes in the hindgut. Infection is probably brought about by the sheep swallowing the whole ked, as the trypanosomes do not appear in the fæces. This species is non-pathogenic.

Trypanosoma lewisi Kent, 1879 is a parasite of the rat all over the world, and is very numerous, as a rule, in the blood-stream (Fig. 193, 11) at the height of an infection. It is generally considered to be non-pathogenic. Individual trypanosomes vary very considerably in size and appearance during the multiplicative phase which passes on in about a week to a chronic phase, in which the trypanosomes measure, on an average, 24 μ . The nucleus is situated slightly anterior to the middle point of the body. The parasite undergoes development in *Ceratophyllus fasciatus*, *Xenopsylla cheopis*, and other fleas, as well as in the rat-louse, *Polyplax spinulosa*. The rat-flea is the chief carrier. The trypanosomes multiply in the hindgut of these insects as crithidial forms and escape as small metacyclic trypanosomes in the excreta. These are ingested by the rat which licks up the flea fæces or devours the entire flea. Trypanosomes appear in the blood after an incubation period of six days.

2. *Leishmania*

The parasites belonging to this genus occur in man in kala-azar, oriental sore, and the muco-cutaneous disease of South America. The parasite of kala-azar is known as *Leishmania donovani*, and that of oriental sore as *L.*

tropica. It is supposed by some that the parasite of Mediterranean kala-azar which is associated with the disease in dogs is a distinct species, *L. infantum*, while that of the South American disease has been named *L. braziliense* and *L. americana*. There is no morphological difference between the parasites from all these diseases, which cannot be differentiated from one another except by certain serological reactions. Probably the tissue changes produced after inoculation into hamsters may indicate specific differences. Hindle has shown that in these animals *L. infantum* produces periartritic swellings of the extremities and tail, thus differing from *L. donovani*. The parasite is a small, round or oval, or, sometimes, cigar-shaped body varying in diameter from 1 to 3 or 4 μ . It consists of a minute mass of cytoplasm enclosed by a delicate membrane. Within the cytoplasm is a nucleus and a kinetoplast consisting of parabasal body and blepharoplast from which runs to the surface of the body a rhizoplast which represents the axoneme of the flagellum of the flagellate and which develops in cultures and in the sandfly.

The parasites in the body occur sometimes in large numbers, in the large endothelial cells, macrophages or clasmatocytes. These cells in kala-azar are found with the contained parasites in all parts of the body, particularly the spleen, bone-marrow and liver and, in oriental sore and the South American disease, in the skin and mucosæ. The parasite, the Leishman-Donovan body, is actually the rounded stage of a flagellate having the leptomonas structure as evidenced by its development into flagellates of this type in artificial culture media or in the sandfly.

Life-history.—The life-history of members of the genus *Leishmania* is essentially that of insect flagellates of the genus *Leptomonas*. A typical form, *Leptomonas ctenocephali* of the dog-flea multiplies in the hindgut as an elongate flagellate and finally produces in the rectum small, round leishmania bodies which escaping in the fæces are eaten by the flea larvæ. In members of the genus *Leishmania* the same leishmania forms occur, but in the tissues of man they multiply by binary fission. It was shown first by Rogers that these forms developed in culture media into leptomonad flagellates like the corresponding stages of the flagellate of the dog-flea. The same change will take place in the stomach of the bug owing to the quantity of blood. Since the successful production of oriental sore in man by the inoculation of crushed up sandflies (*Phlebotomus*) by Sergeant and his co-workers, attention has been directed towards these flies. It has been found that in the stomach of insects of this genus, both *Leishmania tropica* and *L. donovani* taken up from man develop rapidly into the typical elongate leptomonad forms and that these tend to spread forwards to the biting parts of the fly (buccal cavity, proboscis). It has been shown by Adler and Theodor that when such infected flies feed into a sterile fluid through a rabbit-skin membrane, flagellates are injected into the fluid. Both in the sandfly and in N.N.N. culture medium (p. 861), the rounded leishmania form first increases in size and then develops a flagellum. By further growth and active multiplication there is produced the elongate leptomonas form with its long flagellum. In the fly many of the flagellates become attached to the wall of the anterior part of the stomach. On account of the resemblance of the various forms to those of the flagellate in the dog-flea or other insect, certain authorities think that the parasite of kala-azar and oriental sore should be included in the same genus. (*Leptomonas* or *Herpetomonas*.)

The fully-developed elongate flagellates are 14–20 μ in length by 2 μ in breadth. The flagellum is 16 to 24 μ in length. The flagellates move actively with the flagellum in front, and in cultures tend to agglomerate in clusters

(rosettes), the flagella being directed centrally. The culture medium originally used by Rogers was made by adding material from spleen-puncture to slightly acidified citrate-of-soda solution. It is now known that the parasites will grow better in the liquid of condensation of blood-agar medium (N.N.N. medium). A small quantity of infected material from a human case of kala-azar or oriental sore is added to the liquid of condensation. The tubes are incubated at 22–25° C. In two or three days flagellates of various shapes appear in the liquid. These multiply for two to three weeks, after which it is necessary to subculture into fresh tubes if the culture is to be maintained. Cultures may be commenced from any tissues containing parasites, even the peripheral blood, but it is essential that bacterial contamination should be excluded. (Fig. 195.)

Nomenclature of hæmoflagellates.—There are four types of flagellate—



Fig. 195.—Developmental forms of *Leishmania donovani* from the leishman body to the crithidial stage, and clumping of the flagellated organisms. $\times 2,000$. (After Wenyon.)

leishmania, leptomonas, crithidia and trypanosome—names derived from the generic titles. Certain flagellates have only leishman and leptomonas stages. If confined to insects alone, they belong to the genus *Leptomonas*; if occurring in both insects and vertebrates they belong to the genus *Leishmania*. Other flagellates have leishmania and crithidia stages. All these are confined to insects and are included in the genus *Crithidia*. Others again have leishmania, crithidia and trypanosome stages. If in insects alone, they are named *Herpetomonas* and if in both insects and vertebrates, they belong to the genus *Trypanosoma*. The accompanying diagram, after Wenyon, illustrates this point of view (Fig. 196).

3. *Leptomonas*

The distinctive feature of this genus is the adult flagellate stage which is like the flagellate stage of *Leishmania*. There is an elongate body with

central nucleus. Near the anterior end is the kinetoplast from which arises the axoneme of the long anterior flagellum. A typical member of the genus is *Leptomonas ctenocephali* in the dog-flea mentioned above. It passes from flea to flea by leishmania forms voided in the fæces. Certain flagellates which are morphologically of this genus parasitize plants, especially *Euphor-*

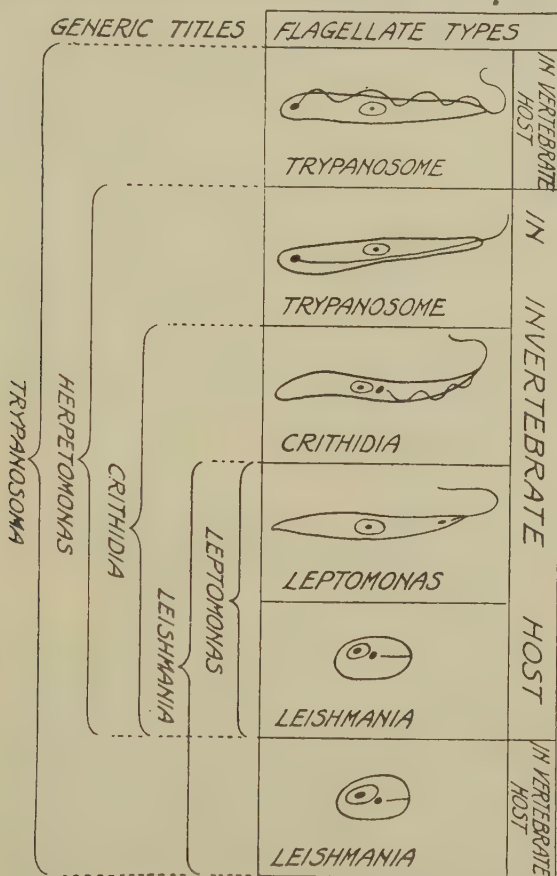


Fig. 196.—Diagram of classification of trypanosomes and allied flagellates. (After Wenyon.)

biaciæ. They live in the latex which becomes profoundly altered, leading to the death of the plant. In one case the infection is spread from plant to plant by a plant bug *Stenocephalus agilis* in which it lives as an intestinal flagellate. It is suggested that these plant flagellates be given the generic name *Phytomonas*.

4. *Crithidia*

The members of this genus have elongated bodies with central nuclei. The kinetoplast lies just anterior to the nucleus while the axoneme passes

to the anterior end of the body along a short undulating membrane. As in members of the genus *Leptomonas*, the flagellates pass from one insect host to another by leishmania forms voided in the fæces.

5. *Herpetomonas*

The members of this genus have leishmania, crithidia, and trypanosome stages in the life-history, but, unlike members of the genus *Trypanosoma*, which show the same forms, they are confined entirely to insects, especially the Muscidae. Infection is spread from insect to insect by leishmania forms passed in the fæces. The flagellate of the house-fly is known as *Herpetomonas muscarum*.

Sandflies (*Phlebotomus*) have been found naturally infected with leptomonas which are probably identical with *Leishmania tropica* and *L. donovani*.

INTESTINAL FLAGELLATES

In addition to forms which are truly parasitic, there are many which appear in stale, decomposing fæces which develop there after the fæces have been voided, owing to cysts which have passed through the intestine. These are actually free-living forms and do not occur in the intestine otherwise than in the encysted state. Protozoa which appear in fæces in that way are known as coprozoic. Such forms amongst the flagellates are various species of *Bodo* (Fig. 197), *Cercomonas*, etc. The form *Cercomonas longicauda* Dujar-

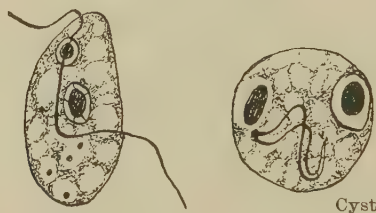


Fig. 197.—*Bodo caudatus*. $\times 2,000$. (After Brumpt.)

din, 1841, has a pear-shaped body and no flagella. The axonemes of both arise from the nuclear membrane on which are two blepharoplasts. When they reach the anterior end of the body one is continued with a long anteriorly directed flagellum, while the other passes backwards over the body to pass into a posterior flagellum. The flagellate is very metabolic and performs amœboid as well as swimming movements. Of the various species of *Bodo* belonging to the family Bodonidae, *Bodo caudatus* Dujardin, 1841, is one which may occur coprozoically in decomposing fæces and also in decomposing urine, if cysts find their way into it.

Bodo caudatus possesses a nucleus and kinetoplast made up of a large parabasal body and two blepharoplasts from which arise the axonemes of the two flagella.

Of the truly parasitic forms there are *Embadomonas intestinalis* and *Chilomastix mesnili*.

Embadomonas intestinalis (Wenyon and O'Connor) 1917 (Fig. 198) is a small, active flagellate of oval shape, $4-9 \mu$ in length and $3-4 \mu$ in breadth, inhabiting the intestinal canal of man. There are two flagella, the anterior being the longer and thinner; the posterior projects from a mouth situated

somewhat laterally at the anterior end. These flagella act independently of each other, thereby imparting a peculiar jerky movement to the organism. In shape it is ovoid, possessing a blunt anterior and a posterior pointed extremity. The cytoplasm is vacuolated and contains ingested bacilli. The round nucleus occupies the anterior end of the body. The cysts are pear-shaped, 4.5-6 μ in length, and when viewed in the fresh state appear to be structureless; when they are stained, certain nuclear structures can be made out.

This parasite has been cultured on egg-medium; it has apparently no pathological significance.

Chilomastix mesnili Wenyon, 1910. Synonym, *Tetramitus mesnili* (Fig. 199).—The parasite also occurs in the large intestine and resembles *Trichomonas hominis* in general shape and size. It has three long anterior flagella, but is devoid of the undulating membrane and axostyle. It possesses a large mouth, occupying two-thirds of the body-length, with a contained flagellum which, in common with the three anterior organs, arises from a granule situated anteriorly to the spherical nucleus. The posterior extremity is

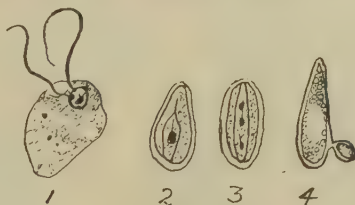


Fig. 198. $\times 2,000$. (After Dobell and Wenyon.)

1, *Embadomonas intestinalis*; 2, 3, cysts of same; 4, yeast organism simulating an embadomonas cyst.

drawn out to a fine point. The cytoplasm is vacuolated and may contain bacteria, which form the food supply. These organisms vary much in length, but average 14 μ in length by 5-6 μ in breadth. Division probably takes place by longitudinal fission. In formed stools the lemon-shaped cysts appear, and vary in length from 7 to 10 μ ; they contain a single nucleus, and show vestiges of a mouth structure as in the free form. In fresh preparations the cysts have to be differentiated from the yeasts of similar size and shape which are frequently present in faeces.

In freshly voided discharges *Chilomastix* has an active, jerky movement, which distinguishes it from the more deliberate rotatory action of *Trichomonas*. Infections with this parasite are very persistent, though there is no evidence that it is pathogenic. Recently it has been cultured on artificial media, as in the case of *Trichomonas hominis*.

ORDER II.—POLYMASTIGINA

Polymastigina usually possess three or more unequal flagella; a distinct mouth-opening and other organs may also be present.

Trichomonas hominis Davaine, 1860 (Fig. 200).—This common intestinal flagellate of man inhabits, often in enormous numbers, the large intestine and caecum. Its body is pear-shaped, 10-15 μ in length by 7-10 μ in breadth. A spherical nucleus is situated at the anterior end, and just anterior to this are placed the blepharoplasts from which arise the long free

flagella; these are directed forwards, while a thicker one passes backwards and forms the border of an undulating membrane, beyond which it is continued as a free flagellum. A small aperture near the anterior end represents the mouth or cytostome. A stiffening rod supports the undulating membrane and arises from the blepharoplast. Running down the middle of the body is a second skeletal rod, known as the axostyle. The cytoplasm is vacuolated and contains bacteria and food granules. According to the number of free flagella (3, 4 or 5) three varieties of *Trichomonas* occur. The one with four free flagella is most commonly encountered.

These flagellates progress rapidly by lashing movements proceeding from the three anterior flagella, while the undulating membrane causes the parasite to revolve on its longitudinal axis. The parasite is also capable of a certain amount of amœboid movement, especially evident in degenerating individuals.

Reproduction is effected by longitudinal fission. When the various organs are completely duplicated, the body of the flagellate splits and gives rise to

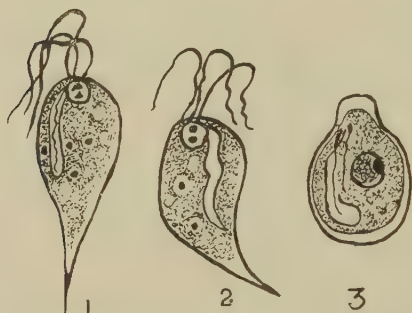


Fig. 199. $\times 2,000$.

1, 2, Active forms of *Chilomastix mesnili*. (After Wenyon and Dobell.)
3, Cyst of the same. (After Dobell.)



Fig. 200.—*Trichomonas hominis*. $\times 2,000$. (After Wenyon and Dobell.)

two daughter individuals. No encysted forms are known, though it seems they must be present at some stage.

The abundance of *T. hominis* in diarrhoeic conditions has led some observers to regard it as pathogenic to man. Wenyon, on examination of material from cases of intestinal infection with this organism, found definite evidence of invasion of the intestinal wall by the flagellates. He has pointed out that guinea-pigs infected with *T. caviae* often show ulceration of the large intestine.

Another species, *Trichomonas buccalis*, occurs in the mouth-cavity and on the surface of the tonsil, and a third, which inhabits the vagina, is known as *Trichomonas vaginalis*, and is found in 10 per cent. of women. According to Wenyon and O'Connor, intestinal infections with *Trichomonas* are very persistent. The parasite may be present for weeks, disappear from the stools mysteriously, and return just as mysteriously at some later period. There is no evidence that it is pathogenic. Its presence in diarrhoeic stools is probably merely a coincidence as it finds in the liquid fæces a congenial

medium for multiplication. In dysenteric stools containing blood these flagellates not infrequently ingest red cells.

Varieties of *Trichomonas* occur; those with three, four or five anterior flagella have been termed *Tri-Tetra-* and *Penta-trichomonas*. *Trichomonas hominis* can be cultivated on blood-agar and Locke's fluid, similarly to *E. histolytica* (p. 865) for many generations. Subinoculations must be made every few days.

Certain flagellates, often included in the order Polymastigina, but sometimes separated as a distinct order Diplomonadida, are peculiar in that they have two nuclei and two sets of organs, giving them the appearance of double flagellates. There are two genera—*Hexamita* and *Giardia*. Only the latter is represented in man, the former occurring in mice and other animals.

Giardia intestinalis Lambl, 1859. Synonyms, *Lamblia intestinalis*, *Giardia lamblia* (Hegner and Taliaferro) (Fig. 201).—This parasite lives in the upper part of the small intestine, particularly the duodenum. In

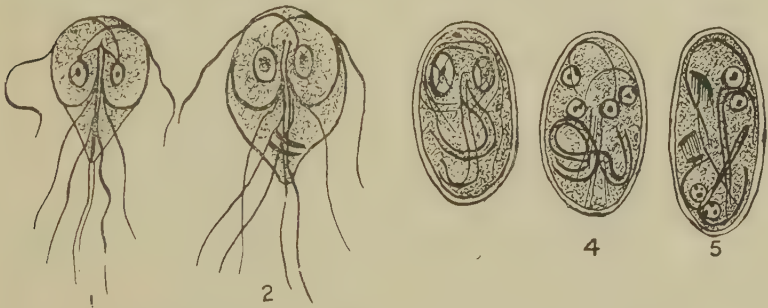


Fig. 201.—*Giardia intestinalis*. $\times 1,800$. (After Wenyon.)

1, 2, Young and adult flagellate forms; 3-5, Cystic stage (3, cyst with two nuclei; 4, cyst with four nuclei; 5, division of flagellate within cyst).

shape it resembles the half of a pear split longitudinally, and it measures 12-18 μ in length by 6 μ in breadth. The ventral surface has a concave sucking disc, with a raised edge, at the anterior end. The posterior extremity tapers into a tail and terminates in two flagella. There are four pairs of flagella, arising from a series of blepharoplasts. Two axostyles pass down the centre of the body. Two oval nuclei are situated at the anterior end. The flagellate swims rapidly, swaying from side to side. *Giardia* reproduces itself by a very complicated process of binary fission. The cysts may occur in enormous numbers in the faeces. At first binucleate, certain complicated changes proceed inside the cyst-wall, which result in the formation of four nuclei, duplication of all the structures, and finally two completely new individuals. The cysts are then very characteristic structures, 14 μ in length. The cytoplasm is quite transparent, and the structures contained therein can be defined with precision. The presence of the axostyles, which form a sort of dividing line within the cyst-wall, gives it a distinctive appearance and serves to distinguish it from cysts of amoebæ (Fig. 201).

Infections are very persistent so that cysts may be found in the stools for many years. Under certain conditions, it is thought by some observers,

this parasite may assume a pathogenic rôle. It is said to have been seen in bile removed from the gall-bladder at operation and is commonly found in the duodenal juice obtained by tubage. It has not been artificially cultured.

Species of *Giardia* occur in rats, mice, cats, dogs and other animals.

CLASS III.—SPOROZOA

This class contains three orders of medical interest :

- i. Coccidia.
- ii. Hæmosporidia.
- iii. Sarcosporidia.

ORDER i.—COCCIDIA

The Coccidia are intracellular protozoa in whose life-cycle there is an alternation of generations in which an asexual cycle, schizogony, alternates with a sexual cycle, sporogony. In the latter a single zygote which becomes encysted as an *oöcyst* eventually produces a number of sporozoites which may be included in groups in smaller cysts, or *sporocysts*.

Life-cycle of a typical coccidium.—The life-history of *Eimeria schubergi* in the centipede *Lithobius forficatus* may be taken as an example, for it was by the study of the allied coccidium of the rabbit that Pfeiffer predicted in such a remarkably accurate manner the life-cycle of the malaria parasite in 1892. The young parasites, or sporozoites, are liberated from a sporocyst in the intestinal tract (Fig. 202, 1) and penetrate epithelial cells, where they grow into large schizonts, characterized by a large vesicular nucleus and a karyosome (Fig. 202). When full-grown the nucleus divides by repeated fission till a variable number of daughter-nuclei are produced (Fig. 202, 2, 3). The schizont now divides into as many merozoites as there are nuclei (Fig. 202, 4). The cells burst, the merozoites are set free, and entering other cells (Fig. 202, 5) develop in one of two ways, either into schizonts again (Fig. 202, 1) or into gametocytes (Fig. 202, 5, 6). The sexes of the latter can be distinguished; in the male (Fig. 202, 6) the protoplasm is clear, but in the female (Fig. 202, 5) it is crowded with reserve food material.

The male gametocyte develops further (Fig. 202, 7); the nucleus divides repeatedly, forming many secondary nuclei, which develop into microgametes (Fig. 202, 8)—small, slender bodies provided with two flagella. The host cell then bursts, liberating the microgametes, which endeavour to enter the female cell or macrogamete (Fig. 202, 8). When one such has effected its entrance, the fertilized macrogamete, which is now the zygote, secretes a tough membrane and becomes an *oöcyst* (Fig. 202, 9), thus effectually preventing the entrance of any other microgametes. The nucleus of the penetrating microgamete fuses with the female nucleus, forming a sinkaryon (Fig. 202, 10). The zygote breaks up into four sporoblasts (Fig. 202, 12), each sporoblast then becomes (Fig. 202, 13) surrounded by a tough envelope, the sporocyst, within which the protoplasm divides to form two sporozoites (Fig. 202, 14). Consequently, when sporogony is complete, the original *oöcyst* contains four sporocysts, each containing two sporozoites (Fig. 202, 14). In order to develop further the *oöcyst* must pass out with the fæces and be swallowed by a new host, whereupon the tough membranes dissolve, liberating the sporozoites (Fig. 202, 15).

Coccidia are common parasites of vertebrates. Since Woodcock and Wenyon's discovery of the *oöcysts* of *Isospora* in human fæces in 1915, and

Dobell's work on the same subject (1919), it is known that at least three different coccidia—one belonging to the genus *Isospora* and two to the genus *Eimeria*—are occasionally found in the faeces of man.

Coccidia occurring in the faeces of man

Isospora belli Wenyon, 1923. (*Isospora hominis*.) (Fig. 203, 1, 2.) More than 150 cases of infection have been recorded with this organism. There is little proof up to the present that, though undoubtedly parasitic in man,



Fig. 202.—Life-history of *Coccidium*. (After Schaudinn.)

1-4, Schizogonic cycle ; 5-15, sporogonic cycle.

it is seriously pathogenic, for even in the most heavily infected individuals no alarming symptoms have been described save in Connal's case. The schizogonic cycle of development in the intestine is unknown. The oöcysts are an elongated oval in shape, with a tapering extremity and vary in length from 18-33 μ , while their length is 12.5-16 μ , the oöcyst-wall is perfectly clear and colourless. These oöcysts are usually discharged with the zygote in an unsegmented condition, but occasionally after its segmentation into sporoblasts. In the faeces outside the body the zygote segments to form two ovoid sporoblasts which quickly become enclosed in sporocysts,

each measuring about $14\ \mu$ in length by $7\text{--}9\ \mu$ in breadth, and each eventually containing four sporozoites.

With regard to the coccidia of the genus *Eimeria*, Gordon Thomson and Robertson have pointed out that these are actually parasites of fish and that the oöcysts are passed unchanged through the human intestine after ingestion. Attention is given to these organisms because they were formerly thought to be parasitic in the human intestine.

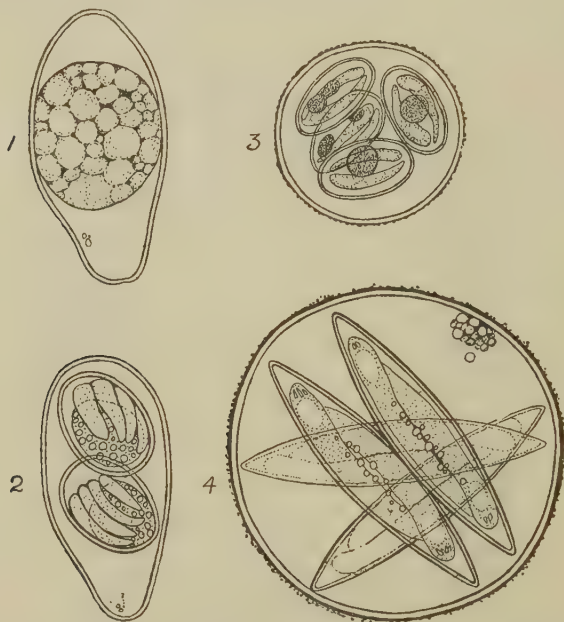


Fig. 203.—Coccidia occurring in man. $\times 1,000$. (After Dobell.)

1, *Isospora belli*, undeveloped cyst. 2, Fully developed spores of same. 3, *Eimeria clupearum*, fully developed oöcyst and spores. 4, *Eimeria sardinae*, fully developed oöcyst and spores.

Eimeria clupearum Theolohan, 1892 (*E. wenyoni* Dobell, 1918) (Fig. 203, 3).—The oöcysts are passed in the faeces with spores and sporozoites fully developed. The oöcysts are approximately spherical in shape, with a diameter of $22\ \mu$; the outer surface is rugose, the inner smooth and lined with a delicate membrane. The four oval sporozoites within the oöcyst-walls measure $10\ \mu$ by $7\ \mu$, and each contains two typical sporozoites. The oöcysts of this coccidium are found in the intestine in 100 per cent. of herrings, mackerels and sprats.

Eimeria sardinae Theolohan, 1890 (*E. oxyzoispora* Dobell, 1918) (Fig. 203, 4). This coccidium has been found in human faeces on several occasions. The spherical oöcysts measure $36\ \mu$ in diameter, and have their contents completely differentiated into four sporozoites. $30\ \mu$ in length by $7.5\ \mu$ in breadth. Each in turn contains two long slender sporozoites.

As in the foregoing species this coccidium occurs in the testes of sprats and to a lesser extent in the soft roes of adult herrings.

ORDER ii.—HÆMOSPORIDIA

This order comprises the following genera, viz. *Plasmodium*, *Hæmoproteus*, *Leucocytozoon*, *Babesia*, *Theileria*, *Hæmogregarina*.

Of these five genera, only one, the malaria parasite, *Plasmodium*, occurs in man. The remaining four occur in the lower animals, and are noticed here on account of the important bearing a knowledge of their life-cycle has on that of the malaria parasite.

I. PLASMODIUM

There are three species of *Plasmodium* which are found in man, viz. *P. vivax* (p. 24), *P. malarie* (p. 25), and *P. falciparum* (*Laverania malarie*) (p. 26).

Closely allied species have been found in the higher apes and in certain monkeys, e.g. *Plasmodium pitheci* in the orang-outang (*Simia satyrus*), *P. kochi* in *Cercopithecus*, *P. inui* in *Macacus*, *P. cynomolgi* in *Inuus cynomolgus*, and *P. brazilianum* in *Brachyurus calvus*. A form, *P. reichenowi*, which produces crescents, has been found in the chimpanzee and the gorilla.

Similar parasites are found in birds, bats, and squirrels and cold-blooded animals such as lizards. In small birds, sparrows and finches, an analogous and pathogenic parasite is known as *Plasmodium* (*Proteosoma*) *præcox*, and in owls and crows as *P. danilewskyi*. Other species have recently been described from birds. In contradistinction to the human parasite, transmitted by anopheline mosquitoes, the bird parasites are transmitted by culicine mosquitoes, such as *Culex fatigans* and *Aedes argenteus*. In the red blood-cell of the bird, certain species displace the cell nucleus, in this manner differing from *Hæmoproteus* (Fig. 204).

A form of pigment-producing parasite is found in the blood of certain



Fig. 204.—*Proteosoma* (*Plasmodium præcox*) from blood of sparrow. $\times 2,000$.
(After Wenyon.)

1-3, Stages of schizogony. 4, Gametocyte.

reptiles and is known as *Hæmocystidium*. The parasites, which are related to *Hæmoproteus* of birds, are of a large size.

The life-cycles of these parasites have been fully considered in relation to the clinical aspects of human malaria in the early chapters of this book (Chapters I and II), but a summary may with advantage be given here.

Summary of the life-cycle of the Plasmodiæ.—The life-cycle is commenced by inoculation of the sporozoites with the saliva of the mosquito in the act of biting. Thus introduced, the sporozoite pierces and enters a red blood-corpuscle and soon becomes converted into a young parasite. Growth takes place at the expense of the cell. After a period of two or three days, the single nucleus, by repeated division, has multiplied to form a variable number of daughter-nuclei. The parasite then produces a corresponding number of merozoites and a mass of residual protoplasm which contains the characteristic pigment. By rupture of the cell, the merozoites escape into the plasma where, by attaching themselves to other red blood-corpuscles, they repeat the cycle. After several generations of merozoites have been produced, certain of them develop into *gametocytes*, or sexual cells, which, when mature, are of the same size as fully-grown *schizonts*, but contain more

pigment granules and possess only a single nucleus. They are of two types, male and female, of which the latter has a dense and deeply-staining cytoplasm. They are capable of further development only if taken up by the specific kind of mosquito. In the male the nucleus divides, and the daughter-nuclei proceed to the periphery of the cell and become nuclei of a number of fine filaments endowed with motile powers, which break free from the cell as microgametes. In the meantime the female gametocyte becomes a macrogamete, and ready for fertilization by the microgamete. The impregnated female gamete, or zygote, is capable of independent movement, and (now termed an oökinete) bores its way through the lining epithelium of the mosquito's stomach, there encysts between the epithelium and the limiting membrane, and becomes an oöcyst. The original nucleus now divides, and the protoplasm segments round the daughter-nuclei, forming a spongoplasm. Eventually the nuclei arrange themselves on the surface of the cytoplasm; from this mass sporozoites are formed, each nucleus acquiring an appropriate quantity of cytoplasm. The oöcyst then bursts, setting free the sporozoites, which contrive to pass into the salivary glands of this insect, whence, with the salivary secretion, they once more enter the blood on which the infected mosquito is feeding. (Fig. 205.)

Description of the technical terms employed.—Certain zoological terms are employed to designate the various evolutionary phases in the development of malaria and allied parasites. As the inappropriate use of Greek-derived terms tends to great confusion, it is thought necessary to append a short glossary:—

(a) The *endogenous* part of the cycle (Fig. 205) begins with the entrance of the sporozoite into the vertebrate host, and embraces all the various stages of the parasite in the blood.

(b) The *exogenous* part of the cycle (Fig. 205) embraces all the evolutionary stages undergone by the parasite, from the time when as a gametocyte it is abstracted from the blood by the appropriate mosquito, until the time when it leaves its definitive host (*see* p. 19) once more as a sporozoite.

(c) The *asexual* cycle (Fig. 205), or *schizogony*, embraces that part of the development of the parasite in the blood from the entrance of the sporozoite into the red cell to the formation of the fully-formed segmenting body (sometimes known as a rosette). Throughout these stages the parasite is known as a *schizont*, while the daughter individuals formed from the parasite are known as *merozoites*; these enter other red cells, and may either repeat the asexual cycle or develop into sexual forms.

(d) The *sexual* cycle (Fig. 205) is a term employed to designate the formation of sexual individuals in the blood, and also to embrace the exogenous part of the cycle already described.

The part of the sexual cycle which takes place in the peripheral blood, i.e. from the ring-stage to the fully developed gametocyte, is known as *gametogony*. The younger sexual cells are known as developing *gametocytes*; the fertilization of the female gamete by the male element is known as *syngamy*; the male and female gametocytes are respectively *micro-* and *macrogametocytes*; the latter, after the extrusion of "polar bodies" (a process known as maturation), become converted into *microgametes*. The males, on the other hand, proceed to give off *microgametes*. The fertilized female cell-individual is termed a *zygote*, which on becoming motile is known as an *oökinete*. All the various phases assumed by the parasite in the mosquito's stomach from oökinete to sporozoite are grouped together under the term *sporogony*. The term *trophozoite* is applied loosely to any of the endocorpuseular stages of

the parasite in the vertebrate, particularly those which are growing into schizonts.

There has been a good deal of speculation as to why certain parasites develop into schizonts, whilst others become gametocytes. The circumstance of the late appearance of the gametocyte is looked upon by some as evidence that the blood, from repeated development in it of swarms of endogenous parasites, has become exhausted as a pabulum, and that, in consequence,

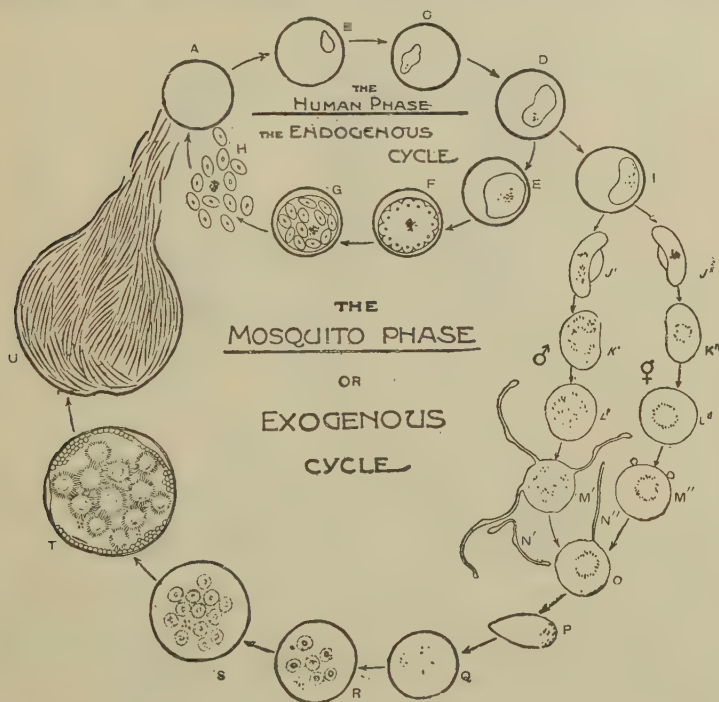


Fig. 205.—Schema showing the human and mosquito cycles of the malaria parasite.

A, Normal red cell; B, C, D, E, red cells containing young parasites; F, G, H, schizogony; I, young gametocyte; J', K', L', M', microgametocytes or male gametes; J'', K'', L'', M'', O, macrogametocytes or female gametes; N', N'', microgametes; P, travelling vermicle; Q, young zygote; R, S, oöcysts; T, oöcyst with plasmodial masses; U, mature oöcyst.

the parasite is directed to a line of development providing for life and growth elsewhere—that is, in the mosquito.

2. HÆMOPROTEUS

Members of this genus (also termed *Halteridium*) are parasitic in the blood of many different species of birds. Within the red blood-corpuscle the sporonts grow into a characteristic dumb-bell-like shape, partially enveloping but not displacing the nucleus. (Fig. 206.) In the halteridium of the pigeon (*Hæmoproteus columbæ*) the sexual cycle is passed in a

hippoboscid fly, *Lynchia maura*, and a development of oöcysts takes place on the stomach of the insect, with subsequent liberation of sporozoites into the salivary glands. Schizogony occurs within the capillary endothelial cells of the pigeon's lung. In these cells the parasites grow and divide into a number of merozoites. Finally the cells burst, setting free the merozoites, which, entering red blood-corpuscles, become typically-shaped gametocytes. The male is easily distinguished from the female by the larger size of its nucleus and by the faintly-staining properties of its protoplasm. Fertilization



Fig. 206.—*Hæmoproteus (Halteridium)* of the kestrel. $\times 1,800$. (After Wasielewski and Wülker.)

Female gametocyte; 2, male gametocyte; 3, male and female gametocytes in same red corpuscle; 4, exflagellation of male gametocyte; 5, female gamete surrounded by male gametes; 6, fertilization; 7-10, oökinetes showing gradual separation of pigment; 11, oökinete with contained pigment.

of the macrogamete occurs in the stomach of *Lynchia* (Fig. 206). An oökinete is formed which penetrates the stomach-wall and produces an oöcyst and sporozoites, which make their way to the salivary glands just as occurs in the case of the parasites of malaria. Members of the genus occur also in cold-blooded vertebrates.

3. LEUCOCYTOZOON

The leucocytozoa are elongated oval bodies (Fig. 207), parasitic in the blood of birds. They modify the shape of the host-cell, which is thought by some to be a mononuclear leucocyte. Peristaltic contractions which pass along the parasite causes the cytoplasm of the host-cell to be driven out into the spindle-like prolongation. Male and female forms are recognized; in the latter the protoplasm acquires a deep stain; no pigment is formed. Schizogony probably takes place in the lung and other organs as in *Hæmoproteus*. "Exflagellation" and fertilization, with the formation of oökinetes,

occur exactly as in the malaria parasite, but the method of transmission and the definitive host are still unknown.

Well-known species are *Leucocytozoon ziemanni* Laveran, 1902, of the little owl, and *Leucocytozoon neavei* Balfour, 1906, of the Sudan guinea-fowl.

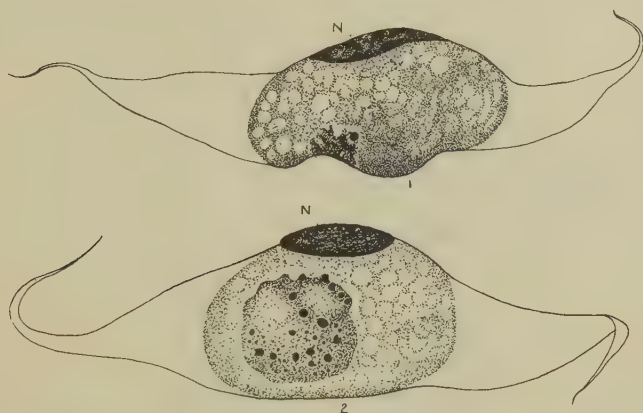


Fig. 207.—*Leucocytozoon neavei* from the blood of the guinea-fowl. $\times 2,000$
(After Wenyon.)

1. Female. 2, male gametocyte. Note distortion of the leucocyte and displacement of cell nucleus (N).

4. BABESIA

This genus, sometimes named *Piroplasma*, comprises a number of minute oval organisms which parasitize the red blood-corpuscles of mammals. No pigment is produced, but the corpuscle is destroyed, the hæmoglobin set free, and ultimately partly excreted by the kidney of the host. The typical babesia is a pear-shaped body dividing by a process of budding, and is found in the red corpuscles of cattle, horses, dogs, sheep, and in a number of other animals. The parasites are transmitted by ticks, *B. bigemina* by species of *Magaropus*, and *B. canis* by *Rhipicephalus sanguineus*. The best-known piroplasms are *Babesia bigemina*, the parasite of red-water or Texas fever of cattle, and *B. canis*, the cause of malignant jaundice of dogs (Fig. 208).



77

Fig. 208.—*Babesia canis*. (After Nuttall.)

Multiplication takes place by budding or gemmation.

B. caballi causes biliary fever in horses; while *B. mutans*, a much smaller form, is, apparently, a harmless parasite in the blood of African cattle. In the blood-corpuscles the parasite bears a striking resemblance to *Theileria parva*. The genus *Babesia* has, for convenience, been divided into a number of subgenera of doubtful validity.

5. THEILERIA

The genus *Theileria* includes parasites of red blood-corpuscles which resemble minute piroplasms (*B. mutans*). Reproduction takes place, however, not by budding within the corpuscles, but by schizogony in the internal organs. The schizonts are revealed by spleen- or gland-puncture, and in stained films appear as blue bodies, dotted over with red nuclei (Koch's blue bodies). The parasite is the cause of a serious disease of cattle "East Coast fever," and is transmitted by ticks, particularly *Rhipicephalus appendiculatus*.

Anaplasma, a small coccoid body in the red cells, was first described by Theiler in cattle. These bodies are arranged either in the centre of the cell or peripherally; hence the names *A. centrale* and *A. marginale* have been applied to them. According to recent investigations they are not parasites at all, but possibly represent a degeneration of the red cell as a result of some invisible virus.

Certain rod-shaped bacilliform bodies (*Grahamella*) have been described in red cells of rats, moles, and gerbilles (Fig. 209), and have been thought

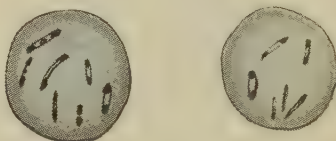


Fig. 209.—*Grahamella*, or bacilliform bodies in red cells of rat, mole, etc. (Orig.)

to be of the same nature as the structures met with in Oroya fever in man and known as *Bartonella bacilliformis* (p. 234), which were cultivated by Noguchi and regarded as a bacillus. Similar bodies appear in the blood of rats after splenectomy (*Bartonella muris*), in animals infected with *Grahamella*.

6. HÆMOGREGARINA

The hæmogregarines are found in all classes of vertebrates, and are especially common in reptiles, amphibia, and fishes, but are also found in certain mammals, such as dogs, rats, and the jerboa. They are sausage-shaped bodies with a large central nucleus, and lie encapsuled in the red blood-cells (*H. balfouri* of the jerboa, and the majority of hæmogregarines of cold-blooded vertebrates), or in the leucocytes' (*Hepatozoon muris* and *H. canis*, Fig. 210, 1, 2). They are not amoeboid, and no pigment is produced. The form seen in the peripheral blood may leave the corpuscle as a free vermicle much resembling a small gregarine in appearance and in its gliding movements. Schizogony does not proceed in the blood, but in some internal organ—in the lungs, spleen or bone-marrow in some animals, but in the case of *H. balfouri* of the jerboa (Fig. 211) in the liver. A variable number of merozoites are produced, and it is these which enter the circulating cells of the blood. They are gametocytes, both male and female, which only develop further in the invertebrate host. In the intestine of the invertebrate the male and female gametocytes unite in pairs, the male producing a number of male gametes. In the case of *Hemogregarina stepanowi* of the tortoise the invertebrate host is a leech. Four microgametes are produced by the male gametocyte, and one of these fertilizes the macrogamete. The zygote then encysts, and grows

into an oöcyst containing sporozoites, which again pass into the tortoise. The exact manner in which this is effected is not known, but in the case of *Hepatozoon muris*, which develops in the rat-mite (*Lelaps echidninus*), producing a large oöcyst containing sporocysts and sporozoites, the mite is



Fig. 210.—Various hæmogregarines. (After Wenyon.)

1. *Hepatozoon muris* of the rat in a leucocyte. 2. *H. canis* of the dog in a leucocyte. 3. Hæmogregarine of the cobra in a red blood-corpuscle. 4. Hæmogregarine of the frog in a red blood-corpuscle. 5. Hæmogregarine of the tortoise in a red blood-corpuscle. 6. Young schizont of *H. canis* in spleen-cell of dog. 7. Fully-grown schizont of *H. canis* in process of budding off merozoites, in spleen of dog. 8. Portion of a cyst of *H. canis* showing several sporocysts with sporozoites in tissues of dog tick (*R. sanguineus*).

devoured by the rat, and the sporozoites, liberated in the rat's intestine, pass through the wall of the gut into the blood-stream, re-enter the liver cells, and become schizonts. In the case of *H. canis*, the dog-tick is the vector, the development being like that of *H. muris* in the mite.

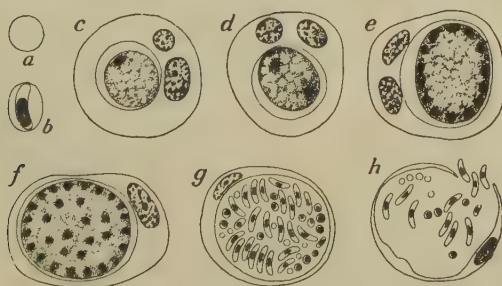


Fig. 211.—*Hepatozoon balfouri*. After (Balfour.)

- a, Normal erythrocyte of jerboa; b, infected erythrocyte; c-h, schizogony within liver-cells.

It is highly probable that various hæmogregarines described from man are merely artefacts due to contamination of blood-films with vegetable organisms, but recently Archibald and Susu have discovered in the spleen of a Sudanese the schizogonic stages of a sporozoon which may be a hæmogregarine or a coccidium.

ORDER iii.—SARCOSPORIDIA

These parasites live in the muscular fibres or connective tissue of vertebrates. They are elongate sausage-shaped bodies consisting of a cuticle within which is a series of spaces enclosing a number of falciform spores. The parasite produces a substance called sarcocystine, which is especially toxic for the rabbit. The cysts, which are visible to the naked eye, are commonly known as Rainey's or as Miescher's tubes, and are frequently found in mammals, but rarely in man, in whom it has been found in the muscles of the heart, larynx and arm. *Sarcocystis tenella* is common in sheep and *S. muris* in mice.

Other Sporozoa.—In addition to the orders considered, the Gregarinida are of interest to the student of tropical medicine as certain members of the



Fig. 212.—*Lankesteria culicis*. (After Wenyon.)

- 1, Two gregarines encysted in Malpighian tube of pupa. 2, Gregarine cyst from Malpighian tubes, showing formation of gametes. 3, Malpighian tube of imago of *Aedes argenteus*, showing liberated gregarine sporocysts.

group are parasitic in the larvæ, pupæ, and imagines of insects; for example, the various stages of *Lankesteria culicis* (Ross, 1898) may be found on dissection of *Aedes argenteus* (*Stegomyia fasciata*). (Fig. 212.) Another form occurs commonly in *Phlebotomus argentipes*.

CLASS IV.—INFUSORIA

One important Infusorian occurs in man—the ciliated protozoon, *Balantidium coli* Malmsten, 1857. This parasite is oval in shape, and is of variable size. It may measure 30–200 μ in length by 40–60 μ in breadth, though the average length is 50–70 μ . There are probably various races, distinguished by their size.

The body is clothed with a thick covering of cilia. There is a large kidney-shaped macronucleus with a small micronucleus approximated to it. The protoplasm contains two contractile and a number of food vacuoles, and there is a definite anteriorly-situated mouth and posterior cytophyge or anus. Nutrition is effected by ingestion of solid particles. The cuticle is longitudinally striated. (Fig. 213, 1.) The parasite reproduces itself asexually by transverse fission. Conjugation takes place by approximation of two individuals and by the exchange of certain nuclear elements; after this has been effected the conjugants separate. Encystment occurs (Fig. 213, 2); the cysts, which are slightly ovoid, measuring 50–60 μ in diameter. They are passed in the fæces.

The parasite has been cultured artificially on human serum diluted with saline and kept at 30–37° C. Frequent subinoculations are necessary.

B. coli sometimes burrows into the submucosa causing a dysenteric condition known as balantidial dysentery (see p. 436). The ciliate is a normal

inhabitant of the large intestine of pigs, and those who are in attendance upon them are liable to infection. It has been found in the mesenteric glands, as well as in the ulcers. It is a very active and obvious parasite, and

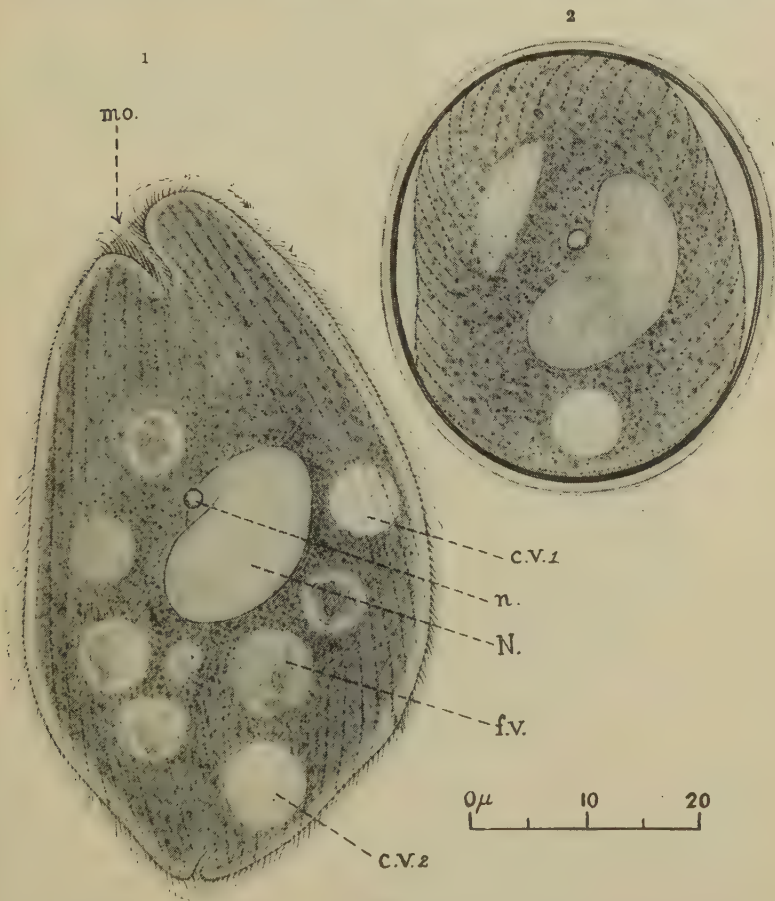


Fig. 213.—*Balantidium coli*. × 1,200.

(After Dobell; by permission of Medical Research Council, Report No. 51.)

- 1, Living animal: N., meganucleus; n., micronucleus; c.v.1, anterior contractile vacuole; c.v.2, posterior contractile vacuole; f.v., food vacuole; mo., mouth.
- 2, Encysted form, showing nuclei, posterior contractile vacuole, and remains of cilia.

may occasionally be found in diarrhœic as well as in blood and mucous stools.

Infection with this organism has been recorded from France, Germany, the Philippines, and elsewhere. The parasite also occurs in monkeys and allied species, in ruminants, and other animals in captivity. It may be the cause of death in monkeys in zoological gardens. Infection is conveyed from one host to another by means of the cysts.

Other Infusoria described from the fæces of man are *Balantidium minutum* and *Nyctotherus faba*, but these are too rare to require description. It is doubtful if they are true parasites.

THE SPIROCHÆTES

Spirochætes are spiral organisms with flexile bodies. In the small slender forms which are parasitic in man it is difficult to make out any accurate details of structure. This is only possible in the larger forms found in the mollusca. These organisms are now regarded as being nearer to plants than to animals, though formerly, on account of the transmission of the blood-inhabiting species by lice and ticks, they were regarded by some authorities as protozoa.

The genus *Spirochæta* Ehrenberg, 1834, includes certain large free-living fresh-water or marine species, of which *Spirochæta plicatilis* is the type. This organism measures up to 500 μ in length and 0.75 μ in breadth. It is a cylindrical filament with regular spirals about 1.5 μ apart. It has an elastic flexible axial filament, and possesses no crista or flagella. (Fig. 214, 1.)

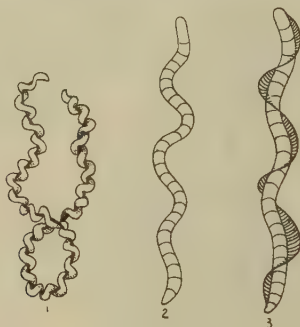


Fig. 214.—Diagram of spirochætes. (Partly after Noguchi.)

1, *Spirochæta* (note axial filament). 2, *Saprospira*. 3, *Cristispira*.

The genus *Saprospira* Gross, 1911, contains large free-living marine and fresh-water spirochætes, of which *Saprospira grandis* is the type. This measures up to about 100 μ in length and 0.8 μ in breadth, and is divided internally into chambers by many transverse septa. The organism is disposed in numerous relatively rigid undulating curves. There are no flagella, nor is there a crista. (Fig. 214, 2.)

The genus *Cristispira* Gross, 1910, is reserved for certain large spirochætes maintaining a parasitic existence in the alimentary tract of oysters and other shell-fish. The type is *Cristispira balbianii*, an organism 45–90 μ in length and nearly 2 μ in breadth, with rounded ends. It is cylindrical in shape and composed of two to five large irregular flexures. It possesses a distinct and flexible longitudinal crest or crista with rudimentary myonemes, and shows an internal chambered structure like the preceding. (Fig. 214, 3.)

The genus *Treponema* Schaudinn, 1905, of which the type is *Treponema pallidum* (Fig. 215, 5), contains species exhibiting a considerable variation in size. The extremities of the organisms are pointed, the spirals wavy and regular. No axial filament is present, and no crista or undulating membrane. The

smaller and finer species, the organisms of syphilis (*T. pallidum*) and of yaws (*T. pertenue*), are composed of numerous regular corkscrew-like spirals of an amplitude of $1\ \mu$. In length these organisms measure 5–14 μ . Similar non-pathogenic species are found in the human mouth (*T. dentium*), throat (*T. vincenti*), intestine (*T. eurygyratum*), in tropical ulcers (*T. schaudinni*), in ulcerating surfaces (*T. refringens*) and elsewhere.

The larger forms of *Treponema* are more flexible and snake-like, and comprise the organisms of relapsing fever (*T. recurrentis*, Fig. 215, 4, *T. duttoni*,



Fig. 215.—Schema of different forms of spirochaetes. $\times 3,500$.
(After Dobell; by courtesy of Wellcome Bur. Sci. Res.)

1. *Leptospira icterohæmorrhagiae* (Inada and Ido) Noguchi. Cause of spirochaetal jaundice (Weil's disease).
2. *Treponema eurygyratum* Werner. Commonly found in human faeces, both in health and in disease (e.g. dysentery).
3. Human red blood-corpusele on same scale.
4. *Treponema recurrentis* Leber (= *Spirochaeta obermeieri* Colin). Occurs in blood in relapsing fever.
5. *Treponema pallidum* (Schaudinn) Vuillemin (= *Spirochaeta pallida* Schaudinn). Syphilis.
6. *Treponema gracile* Levaditi and Stanesco. Found on external genitalia, in health and in various diseased conditions.
7. *Treponema refringens* Schaudinn (emend.) Occurs in syphilitic lesions on external genitalia.

T. persicum, etc.) in man; and *T. anserinum* and *T. gallinarum*, the cause of spirochaetosis in geese and fowls. The human forms are transmitted by ticks (*Ornithodoros*) or lice; the bird ones by ticks (*Argas*).

All these organisms progress by a corkscrew action resulting from revolution on the longitudinal axis.

The genus *Leptospira* Noguchi, 1917, includes the type organism, *Leptospira icterohæmorrhagiæ* (Fig. 215, 1). These organisms measure 7-14 μ in length, with pointed ends, and a spiral amplitude of 0.45 μ , with one or more gently undulating curves. There is no terminal filament, axial filament or undulating membrane, but very frequently the end is bent in the form of a crook. Three pathogenic species have been recognized—*L. icterohæmorrhagiæ* of Weil's disease; *L. hebdomadis* of seven-day fever; and *L. icteroides*, described by Noguchi, in yellow fever (see p. 193). As regards the last-named, considerable doubt has arisen. It now appears that it is identical with *L. icterohæmorrhagiæ*, and is not the cause of yellow fever.

L. icterohæmorrhagiæ is found commonly in the urinary tract or liver of rats and possibly occurs as a free-living form in water (Zuelzer), while Buchanan has found it in the slime on the roof of a mine in Scotland. The form in rats like that in man is highly pathogenic to guinea-pigs.

L. hebdomadis is found as a natural infection in the field-vole, *Microtus montebelloi*.

Simple division transversely into two, is the usual method of reproduction of spirochætes. A peculiar method of spore-formation has been described in *Cristispira* and *Saprospira*, but is not known to occur in other genera. No sexual phenomena are known in any spirochæte and the life-histories of all appear to be very simple. Some observers maintain that spirochætes may break up into minute granules (granular phase) which are able to regenerate spirochætes.

The organism of rat-bite fever, formerly known as *Spirochæta morsus-muris* (p. 216), is no longer considered (Robertson, Dobell, etc.) to be a spirochæte, but a spirillum. The correct terminology of this parasite should be *Spirillum minus* Carter, 1887; synonyms, *Spirochæta laverani* Breinl and Kinghorn, 1906; *Spirochæta muris* Wenyon, 1906.

III. MEDICAL HELMINTHOLOGY

SYSTEMATIC helminthology comprises a study of two phyla of the Animal Kingdom—Platyhelminthes and Nemathelminthes.

The former is divided into three large classes : (1) Turbellaria, (2) Trematoda, (3) Cestoda. The two latter only need be considered, as they contain all the genera parasitic in man.

The parasitic Nematoda are included in the phylum Nemathelminthes, and will be considered later.

TREMATODA

Platyhelminthes with unsegmented, flattened, leaf-like, or rarely, cylindrical bodies. A mouth is present, and one or more suckers, the posterior of which serves as an organ of attachment, while the anterior is alimentary in function (Fig. 217).

The intestine is bifurcated, and both branches usually end blindly.

Reproductive system—The Trematoda are mostly hermaphroditic, though the schistosomes present an exception to this rule. The male and female genitalia both open by a common genital pore, which is usually situated on the ventral surface of the body near the anterior end and in the midline.

Male organs.—These consist of a pair of round, lobed, or branched testes, from each of which pass out vasa deferentia, that unite to form a seminal vesicle ; this, in turn, communicates with a cirrus sac ; the cirrus, which is the protrusible or terminal penis, may, or may not, be present.

Female organs consist of a round, lobed, or branched ovary, a receptaculum seminis, vitellaria or yolk-glands, a shell-gland, and uterus. The ovum itself, after passing from the ovary, enters the oviduct and is fertilized by a spermatozoon from the receptaculum seminis ; at this point it is furnished with yolk-cells from the vitellaria, and passes on through the shell-gland, where it is provided with its outer covering or shell. The finished egg, after travelling through the coils of the uterus, passes out through the uterine opening of the common genital pore. Frequently the receptaculum seminis communicates with the exterior by a short duct which is known as Laurer's canal ; the opening of this canal is in the midline on the dorsal surface of the body. Laurer's canal functions as a vagina and serves for the entrance of spermatozoa received in copulation.

All the organs are embedded in parenchymatous tissue.

Life-history.—The flukes may complete their life-cycle by two distinct methods ; they are therefore divided into two main orders : (1) *Monogenea*, in which no intermediary host is necessary, the non-ciliated larva changing directly into a sexual hermaphroditic animal ; (2) *Digenea*, in which the ciliated larva enters into one or more intermediary hosts—molluscs, crustacea, or fishes.

When laid, the egg may contain a fully-formed ciliated embryo or *mira-cidium* (Fig. 216, 1), or this may take some time to develop. On being liberated

from the shell, either by rupture of the egg-shell or through an *operculum* (which is usually present), the embryo swims actively about in search of an intermediate host in which to carry out the second stage of its development. In the liver, or digestive organ of the intermediate host—generally a fresh-water mollusc—the miracidium loses its ciliated covering and becomes a sac-like body, or *sporocyst*. (Fig. 216, 2.)

This may give rise (a) to the infective stage or *cercaria*, (b) to other

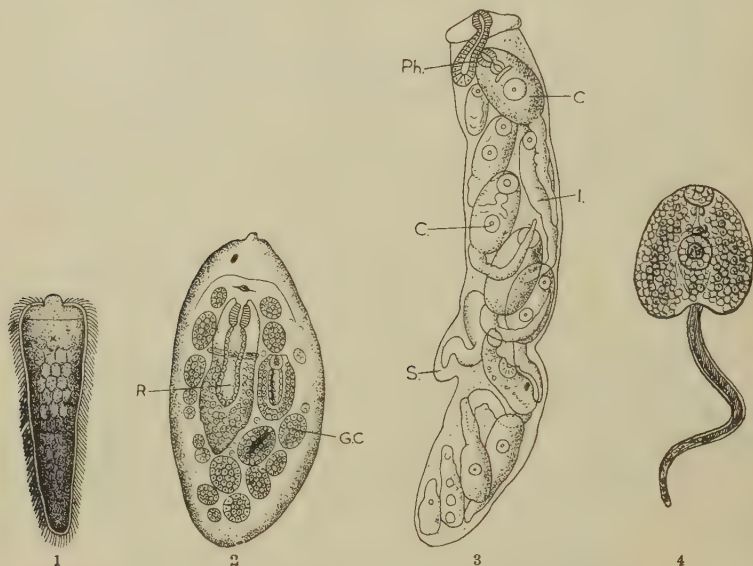


Fig. 216.—Stages in life-history of *Fasciola hepatica*.

(After Thomas and Leuckart, in Brumpt's "*Précis de Parasitologie*.")

1. Miracidium. 2. Development of rediæ (R) of *F. hepatica* inside sporocyst (g.c., germinal balls).
3. Mature redia containing fully-formed cercariæ (C): I., intestine; Ph., pharynx; S., stamp-like projection. 4. Free cercaria containing cystogenous cells.

sporocysts called *daughter-sporocysts*, (c) to *redia*, which are elongated bodies provided with an oral sucker and a rudimentary intestine. (Fig. 216, 3.) From the daughter-sporocysts and *redia* cercariæ are produced. In the life-history of certain flukes a further stage takes place in the *redia*, and daughter-*redia* result; these in turn give rise to cercariæ.

The cercaria (Fig. 216, 4) is the larval stage of the trematode, which is infective to the definitive host. As a rule, cercariæ are provided with one or more suckers, and a tail which is used for swimming.

On attaining full development the cercariæ are set free from the liver, or digestive gland of the snail, and enter the water, in which they can maintain a free existence for about forty-eight hours. In some cases they shed their tails and pierce the skin of the definitive host (e.g. the schistosomes), while in others they encyst in some other organism, either animal, plant, or fish, which may be used as food by the host, e.g. *Paragonimus*, *Fasciolopsis*.

In the stomach of the definitive host the cyst-wall is digested, and the

cercariae, being set free, migrate to their site of election, either the lung, liver, intestinal canal, or, in some instances, the blood-stream.

The **alimentary canal** consists of a mouth situated in the oral sucker, a muscular pharynx, which may be absent, and a thin-walled œsophagus which divides posteriorly into two blind intestinal cæca. Food consists of blood, cells, bile, etc., according to the habitat.

The **nervous system** consists of two large supra-œsophageal ganglia joined by a transverse commissure. From these there pass out two large backwardly-directed ventral nerve-trunks, communicating one with another by transverse anastomoses.

Excretory system.—Throughout the body are scattered numerous “flame-cells,” connected with small channels leading into main ducts, which in turn open into an excretory vesicle situated in the median line; this vesicle discharges by an excretory pore, usually situated at the end of the body.

TREMATODES PARASITIC IN MAN

FASCIOLIDÆ.

Fasciola. Intestinal cæca branched.

F. hepatica.

Fasciolopsis. Intestinal cæca simple.

F. buskii.

OPISTHORCHIDÆ.

Clonorchis. Testes posterior to ovary and racemose.

C. sinensis.

Opisthorchis. Testes posterior to ovary and lobed.

O. felineus.

HETEROPHYIDÆ.

Heterophyes. Genital pore armed and posterior to ventral sucker.

H. heterophyes.

Loxotrema. Genital pore unarmed, anterior to ventral sucker, which is displaced laterally.

L. ovatum.

TROGLOTEMIDÆ.

Paragonimus. Vitellaria numerous and widespread. Excretory vesicle bisects body longitudinally.

P. westermanii.

P. ringeri.

SCHISTOSOMIDÆ.

Schistosoma. Sexes separate; pharynx absent; testes numerous; eggs not operculate; gut branches reunite to form a single cæcum.

S. hæmatobium.

S. mansoni.

S. Japonicum.

PARAMPHISTOMIDÆ.

Gastrodiscoides. Pharyngeal pouches present; body divided into anterior elongated and posterior discoidal portion.

G. hominis. Genital pore on anterior elongated portion.

For illustrations of eggs of trematodes parasitic in man, see Pl. XXXV.

FASCIOLA HEPATICA (Linn., 1758)

The liver fluke has been reported in man as an erratic infection on twenty-eight occasions—in the liver, the portal veins and in subcutaneous abscesses. It is said to occur in the Lebanon as a bucco-pharyngeal infection, where it is locally known as "halzoun."

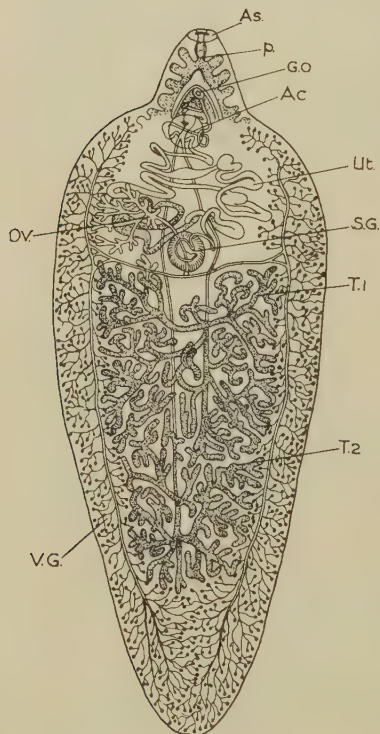


Fig. 217.—*Fasciola hepatica*. $\times 4$.

(Partly after Sommer, in Brumpt's "Précis de Parasitologie.")

Posterior branching of intestine is not shown.
(For lettering, see p. 715, footnote.)

F. hepatica (Fig. 217) is a parasite of herbivorous animals, especially sheep, in which it causes the disease known as "liver rot." In colour pale-grey with dark borders; length, 20–30 mm.; breadth, 8–13 mm. The anterior extremity, which bears the oral sucker, is narrow; the posterior, rounded. The ventral sucker is the larger of the two, and is situated 3 mm. from the anterior extremity. Both branches of the intestinal caeca are furnished with many diverticula radiating outwards. The ovary is racemose, and lies in front of the testes, which occupy most of the posterior part of the body.

The uterus lies in front of the ovary, and is short in comparison to the rest of the body; an exsertile cirrus is present. The genital pore is median, half-way between the oral and ventral suckers.

The eggs measure 130–145 μ in length by 70–90 μ in breadth; they are ovoid and operculated, and usually of a brown colour due to bile-pigment. The egg, when passed, contains an ovum and yolk-cells.

The life-history of this fluke was first worked out by Thomas and Leuckart in 1883. A ciliated miracidium develops in the egg in about three weeks, and on escaping finds its way into fresh-water snails of the

genus *Limnaea*. In Europe the species is *L. truncatula*; in Japan *L. pervia*. Large specimens, measuring 75 mm. in length, are called *F. gigantica*, but are probably a variety of *F. hepatica*.

The most important method in the prophylaxis of liver-fluke infection is the employment of a very weak solution of copper sulphate (1 in a million) which kills the intermediate host and is harmless to domestic animals and man, but lethal in this strength to fish.

FASCIOLOPSIS BUSKII (Lankester, 1857)

Habitat.—The parasite lives in the small intestine of man—has even been found in the stomach. In certain parts of China 5 per cent. of the inhabitants are found infected, but only a small percentage of these show characteristic symptoms.

Geographical distribution.—*F. buskii* is an Asiatic trematode, having been reported from India, Assam, the Straits Settlements, Sumatra, Borneo, and China. The pig is the normal host and acts as the reservoir of the infection in man.

Characters.—This trematode is the largest which is parasitic in man (Fig. 218). The average length is 30 mm., breadth 12 mm., and thickness 2 mm. It is a thick, flesh-coloured fluke of elongated oval shape, narrower anteriorly than posteriorly. The cuticle on the ventral surface is covered with spines arranged in transverse rows, most numerous in the region of the ventral sucker. The oral sucker (0.5 mm. in diameter) is subterminal and placed on the ventral surface. The ventral sucker is larger (1.6–2.5 mm. in diameter), and placed close to the oral. It is prolonged into a kind of sac (2–8 mm. long) directly under the ventral surface. The pharynx (0.7 mm. long) is preceded by a prepharynx (0.28 mm. long); the oesophagus is very short, and the intestinal caeca are simple and present two characteristic curves towards the middle line, one at about the middle of the body, the other between the testes. The genital pore opens on the median line immediately anterior to the ventral sucker. The testes are in the posterior half of the body, one behind the other; both are branched dichotomously. The ovary is branched, and is placed about the middle of the body on the right of the median line. The vitellaria are well developed, and extend from the ventral sucker to the caudal end of the body, where they meet. Their acini are very small. There is a fine tortuous Laurer's canal. The eggs (Plate XXXV, 1, facing p. 874) are numerous, and measure 120–130 μ in length by 77–80 μ in breadth; they are closed by a very delicate operculum.

Life-history.—The evolution of this parasite in a mollusc is in the main similar to that of *F. hepatica*, and was worked out by Nagakawa (1920). After the egg has lain in water for two or three weeks a ciliated miracidium, with two pigmented eyespots and two flame-cells, escapes and enters the body of species of Planorbis—*P. cœnosus*, *P. schmackeri*, *P. (segmentina) largillierti* and *P. nitidella* (Barlow); it then becomes transformed into a sporocyst, within which, in three or four days, rediae develop, these in turn giving rise to cercariæ. The cercariæ, on becoming free in the water, encyst on fresh-water plants, especially the water-calthrop and the water-chesnut

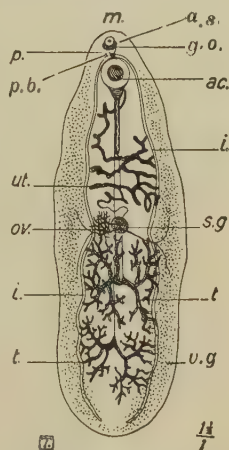


Fig. 218.¹—*Fasciolopsis buskii*. (After Odhner.)

¹ The following is a key to the terminology of anatomy of trematodes, as illustrated in this and other figures: *a.s.*, anterior sucker; *m.*, mouth; *p.*, pharynx; *p.b.*, pharyngeal bulb; *ac.*, acetabulum or ventral sucker; *g.o.*, genital opening; *ut.*, uterus; *v.g.*, vitelline glands; *ov.*, ovary; *s.g.*, shell-gland; *va.*, vagina; *oo.*, oötype; *ovd.*, oviduct; *v.s.*, vesicula seminalis; *r.s.*, receptaculum seminis; *t.*, testis; *v.d.*, vas deferens; *æs.*, oesophagus; *i.*, intestine; *i.c.*, branch intestine; *ex.p.*, excretory pore; *n.c.* nerve cord; *l.c.*, Laurer's canal.

(*Eleocharis tuberosus*) which are fertilized with night-soil and are raised in shallow ponds in which the snails congregate. A period of forty-nine days elapses from the date of infection of the snail to encystment. Infection is acquired through eating cercariæ encysted on these raw vegetables. These are of the leptocercous distome type; the body measures 0.23 mm. in length by 0.15 mm. in breadth, while the tail exceeds it in length by two or three times.

Pathogenesis and treatment.—*F. buskii* inhabits the upper part of the small intestine. Goddard reports that a few flukes cause no inconvenience beyond slight asthenia and anæmia, but that when many are present they cause diarrhœa, with the passage of light-yellow offensive stools. In the later stages the anæmia becomes more intense, and is accompanied by ascites and general œdema. The best treatment is to give thymol or eucalyptus oil, in the same manner as in ancylostomiasis. Recently Barlow has advocated carbon tetrachloride as being the most efficacious drug.

CLONORCHIS SINENSIS (Cobbold, 1875)

Habitat.—This fluke lives in the biliary passages of man, and of dog, cat, pig, rat, mouse, camel and badger. The pancreas and its ducts may be infected; it is rarely found in the duodenum, and never in the gall-bladder (Oppenheim).

Characters.—*C. sinensis* (Fig. 219) is a common parasite of man in the Far East. It occurs as a natural infection in the dog and cat in China. It

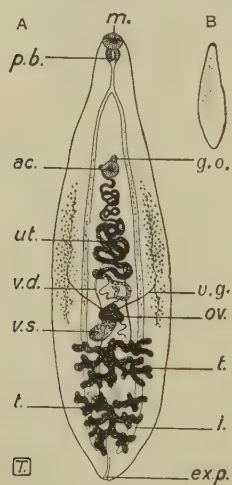


Fig. 219. — *Clonorchis sinensis*. (Partly after Looss.)

A, Magnified; B, natural size.

(For lettering, see p. 715, footnote.)

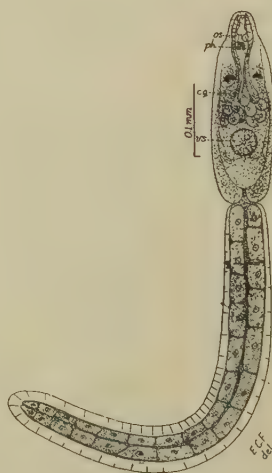


Fig. 220. — Cercaria of *Clonorchis sinensis*. (After Faust and Khaw. By permission of "The American Journal of Hygiene.")

os. = oral sucker. ph. = pharynx. cg. = cephalic secretory-gland. vs. = ventral sucker.

measures 10–20 mm. in length by 2–5 mm. in breadth, is oblong, narrow, flat, and somewhat pointed anteriorly, reddish in colour, and nearly transparent. The oral sucker (0.6 mm.) is larger than the ventral (0.4 mm.), which is situ-

ated between the first and second fourths of the body. The cuticle has no spines. The pharynx is globular and short (Fig. 219, *p.b.*), the œsophagus slender and 0.17 mm. long. The intestinal cœca are simple; the genital pore opens on the middle line immediately in front of the acetabulum. The testes are branched, and situated in the posterior portion of the body, one behind the other. The ovary is trilobate, and its coils are anterior to the genital glands. The vitelline glands are moderately developed, and occupy about the middle third of the body. The eggs are 28–30 μ in length by 15–17 μ in breadth, operculated, almost black, contain a ciliated miracidium (Plate XXXV, 5, facing p. 874), appear to be susceptible to desiccation, and cannot withstand decomposition. According to Nagano the egg does not normally hatch in water, but must be actually ingested by the snail before the miracidium can escape.

Life-history.—Muto has traced development incompletely in *Bythinia striatula* var. *japonica* (Pilsbury). Sporocysts form in two to three weeks, and give rise to cercariæ which, escaping from the snail, encyst on the muscles of certain Japanese fresh-water fish of the family Cyprinidæ, *Pseudorasbora parva*, *Leucogobio güntheri*, and *Carassius auratus*, the latter of which is the more important, as it is commonly eaten pickled or incompletely cooked with soy sauce. Faust has recently shown that all species of Cyprinidæ, Gobiidæ and Anabantidæ are susceptible. At first the cercaria (Fig. 220) secretes a viscous fluid that forms an inner true cyst and is afterwards encapsuled by a fibrous layer formed by the tissues of the fish. The encysted cercariæ (metacercariæ) can withstand a temperature of 50-70° C. for 15 minutes. The cyst-wall is digested in the stomach, while the metacercariæ escape into the duodenum and attach themselves to the mucosa in the region of the opening of the common bile-duct. The young distomes are provided with spines which soon disappear, and they attain maturity in 26 days, when the eggs can be found in the fæces of cats, dogs, rabbits and guinea-pigs fed on infected fish.

For pathogenesis, see p. 584.

OPISTHORCHIS FELINEUS (Rivolta, 1884)

The normal hosts of this species are the dog, cat, glutton and pig. It occurs quite commonly in man in East Prussia, Siberia, Annam, and the Philippines.

This fluke measures 8-11 mm. in length by 1.5-2 mm. in breadth. The cuticle is smooth, the suckers are of equal size, and separated from each other by one-fourth of the body-length. (Fig. 221.) The eggs are small, yellowish-brown; 30 μ long by 12 μ broad. (Plate XXXV, 4, facing p. 874.)

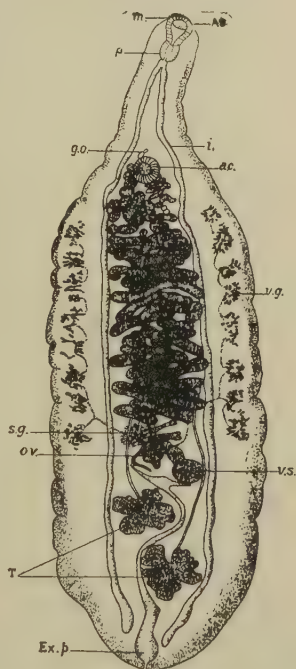


Fig. 221.—*Opisthorchis felineus*. $\times 9$.

(After Barker, in "Archiv de Parasitologie.")

(For lettering, see p. 715, footnote)

Life-history.—The development, according to Askanazy, takes place in a fresh-water mollusc, *Dreysena polymorpha*. According to Ciurea, in Roumania, the ripe cercariæ, measuring 0·34 mm. by 0·24 mm., encyst in fresh-water fish, the bream, *Abramis brama*, the tench, *Tinca tinca*, the chub, *Idus melanotus*, the carp, *Cyprinus carpio*, and the barbel, *Barbus barbus*. The infection is contracted by man through eating raw fish. This species does not appear to be specially pathogenic to man, although 200 or more have been found in the liver and bile-ducts at two autopsies.

Two other species of the genus *Opisthorchis* have been recorded in man, but are of no importance—*O. noverca* and *O. viverrini*, the former from India, the latter from Siam. The normal host of *O. noverca* is the dog, that of *O. viverrini* is the civet cat.

HETEROPHYES HETEROPHYES (Siebold, 1852)

Habitat.—This species inhabits the small intestine, often in very large numbers, and may cause diarrhœa (Low).

Geographical distribution.—*H. heterophyes*, described in 1851 by Bilharz

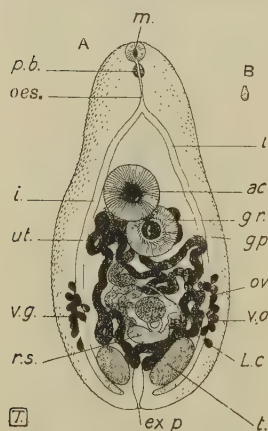


Fig. 222.—*Heterophyes heterophyes*.

A, Greatly magnified; B, natural size.

(For lettering, see p. 715, footnote.)

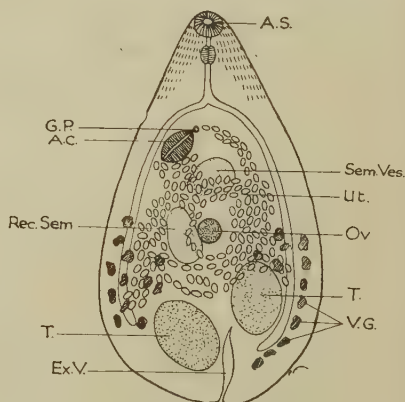


Fig. 223.—*Loxotrema ovatum*. $\times 45$.
(Partly after Leiper.)

Sem. Ves., seminal vesicle; Rec. Sem., Receptaculum seminis; G.P., genital pore. (For other lettering, see p. 715, footnote.)

in Cairo, probably has a wide distribution, and has been reported from Egypt, China, and Japan. Under natural conditions it infests the fox, dog, wolf and cat.

Characters.—*H. heterophyes* (Fig. 222) measures 1–1·7 mm. in length by 0·3–0·7 mm. in breadth. It has an oval, elongate shape, and when passed and fresh is grey, the uterus showing up as a brown patch in the centre of the body. The oral sucker (0·09 mm. in diameter) is subterminal, and about one-third the size of the ventral sucker (0·23 mm.), which is placed at about the middle of the body. The cuticle is thickly set with quadrate scales, 5–6 μ long by 4 μ broad. The prepharynx is short (80 μ in length); the pharynx measures 50–70 μ in length by 40–50 μ in diameter. The œsophagus is about

three times as long. The intestinal cæca extend to the posterior extremity, where they converge and terminate close to the excretory vesicle. The vitelline glands are arranged in two clumps at the posterior end of the body. The genital pore opens postero-laterally to, and in the immediate vicinity of, the ventral sucker; it is surrounded by a muscular ring, and is armed with about 70 antler spines. The testes are oval, and situated posteriorly. The ovary is globular, median, and anterior to the testes. The receptaculum seminis is as large as the ovary; the uterine coils are not numerous, and extend between the ventral suckers and the testes. The eggs are light-brown, thick-shelled, oval, 20-30 μ by 15-17 μ , and contain a ciliated embryo when oviposited. (Plate XXXV, 3, facing p. 874.)

Life-history.—The mollusc which acts as the first intermediary is unknown, but Onji and Nishio, and Khalil in Egypt, have found that infection is acquired from eating raw fish of the species *Mugil cephalus*.

LOXOTREMA OVATUM (Kobayashi, 1908)

Synonym.—*Metagonimus yokogawai*.

Habitat and geographical distribution.—Formerly known as Yokogawa's fluke, *L. ovatum* occurs commonly in the small intestine of natives of Korea, Formosa, and Japan; it is also common in cats, dogs and pigs in China.

Characters.—It measures only 1.1 mm. long by 0.42-0.7 mm. broad; the cuticle is covered with small spines; it is the smallest fluke which occurs in man.

It differs from other members of this class in having the ventral sucker, or acetabulum, displaced somewhat laterally on the left side. The common genital pore lies immediately in front of the ventral sucker. (Fig. 223.) The testes are ovoid and are situated in the posterior third of the body. The ovary and the receptaculum seminis lie immediately in front of the testes in the midline. The yolk-glands are arranged in clumps in the posterior third of the body, and the uterus occupies the space which lies between the testes and the ventral sucker. A large seminal vesicle is present, and lies immediately in front of the ovary. The egg resembles that of *Clonorchis sinensis* in size, but is more regularly ovoid in shape (see Plate XXXV, 6, facing p. 874); it measures 33 μ in length by 21 μ in breadth.

Life-history.—There are two intermediary hosts—a fresh-water snail, *Melania libertina*, in which the redial and cercarial stages occur, and a fresh-water fish, *Plecoglossus altivelis*, under the scales of which the cercariæ have been found to encyst.

The fish is often eaten in a raw state by the Japanese. In some districts of Japan 50 per cent. of the snails are infected with the cercariæ of this parasite.

Pathogenesis.—*L. ovatum* is an apparently innocuous parasite in man, causing at the most a catarrhal condition of the intestinal tract which it inhabits.

PARAGONIMUS RINGERI (Cobbold, 1880), and Allied Species, P. WESTERMANII and P. COMPACTUS

Habitat and geographical distribution.—*P. ringeri* would seem to be confined to China, Japan and Korea. In man, the dog, fox, wolf, panther and cat, it is found in the lungs.

Characters.—*P. ringeri* (Fig. 224) is oval in shape, reddish-brown in colour, and somewhat translucent; so thick is it that it is almost round in transverse section. It measures 8–20 mm. in length by 5–9 mm. in breadth. The anterior extremity is bluntly rounded, without a cephalic cone. The oral sucker (0.88–1.12 and 0.80–0.83 mm.) is terminal or subterminal. The ventral sucker, slightly larger than the oral, is situated somewhat anteriorly to the middle of the body. The pharynx is present and the œsophagus is short, so that the bifurcation of the intestine is considerably anterior to the ventral sucker. The intestinal cæca run a zigzag course towards the caudal end of the body. The common genital pore opens close to the posterior margin of the ventral sucker. The whole of the body is divided into two halves by the large excretory vesicle which lies in the long axis. The testes are tubular racemose glands, and are situated on each side of the middle line in the

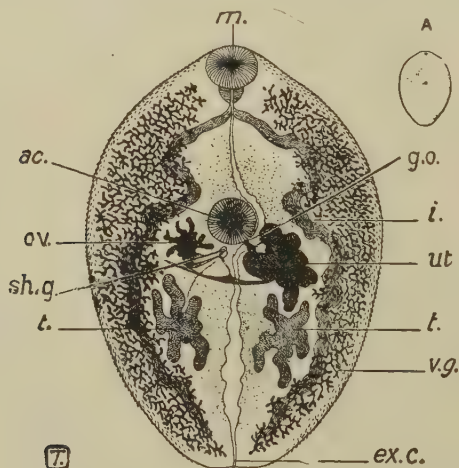


Fig. 224.—*Paragonimus ringeri*. (Partly after Looss.)

A, Nat. size. (For lettering, see p. 715, footnote.)

posterior third of the body. The ovary is branched, and may lie either to the right or the left of the midline, just posterior to the ventral sucker. The uterus is short and somewhat sac-like, and lies opposite to the ovary on the other side of the body. The vitellaria are greatly developed, and extend throughout the whole length of the body. Laurer's canal and a large shell-gland are present. The cuticle is studded with groups of wedge-shaped spines; these groups may vary in number from three to twelve, according to their position. The spines are the only reliable structures by which this can be differentiated from the closely-allied species which occur in man—namely, *P. westermanii*, in which the spines are arranged singly, and *P. compactus*, in which they are arranged in clumps—but they are fewer in number, pointed, and not wedge-shaped as in *P. ringeri*.

The egg of *P. ringeri* measures, on an average, 90 μ in length by 55 μ in breadth. It is operculate, brown in colour, and there is a slight thickening at the opposite pole to the operculum. (Plate XXXV, 2, facing p. 874.)

The egg of *P. westermanii* is slightly smaller, and measures 85 μ in length

by 55 μ in breadth, while that of *P. compactus* is smaller still, and measures 75 μ in length, and on an average 48 μ in breadth. Neither of these eggs has so marked a thickening at the opposite pole to the operculum as has the egg of *P. ringeri*.

The geographical distribution of these three species is also somewhat different. *P. ringeri* would seem to be confined to China, Japan and Korea, whereas in India and in the Malay States man is liable to be infected with *P. compactus* and *P. westermanii*. A fourth species occurs in the pig, dog, and cat in North America, and in the tiger in the Malay States; it is known as *P. kellicotti*, and up to the present has not been recorded from man.

Life-history (Fig. 225).—On escape from the egg, the miracidium enters a fresh-water snail of the genus *Melania*, of which at least six species¹ have been



Fig. 225.—Life-history of *Paragonimus ringeri*. Figs. 3–9, $\times 15$.

(After Nakagawa, "Journ. Exp. Med.," by permission.)

- 1, 2, First intermediary hosts, *Melania libertina* and *M. obliquegranulosa*, quarter nat. size; 3, 4, cercaria and sporocyst of *P. ringeri*, in *Melania*; 5, 6, 7, tailless cercaria and encysted cercaria in liver of crab as second intermediary host; 8, fully-grown encysted metacercaria; 9, adolescent paragonimus, 14 days old.

found to serve as intermediary hosts (including *M. libertina*, *M. obliquegranulosa*, *M. paucicincta*, and *M. gottschei*), wherein it undergoes the usual developmental changes of sporocyst and redia, eventuating in the formation of cercariae. The cercariae in due time escape into the water and bore their way by means of the stylet into certain species of fresh-water crustacea—*Potamon obtusipes*, *Sesarma dehaani*, *Potamon dehaani* (Fig. 226), *Eriocheir japonicum* (Fig. 227), *Astacus japonicus*, and in Korea, *Eriocheir sinensis* and a crayfish, *Cambaroides similis*. In these the cercariae encyst themselves in the liver, muscles, etc., and especially in the gills. In Japan, man is commonly infected by eating the raw flesh of crustacea. In Korea and Formosa, however, where paragonimiasis is very common, uncooked crabs are not eaten. One is therefore led to suppose that encystment in the crustacean is not a biological necessity for the parasite; it may be that the cercariae gain their entrance to the body in some other vehicle, such as drinking-water.

The pathogenesis is fully detailed at p. 582.

¹ There are four additional species of *Melania* in Korea which are assumed by Kobayashi also to be intermediary hosts.

Other members of the Trematoda have been recorded from man, but are of such infrequent occurrence as to be of little practical importance to the



Fig. 226.—*Potamon* (*Geotalphusa*) *dehaani*. Half nat. size.

student of Tropical Medicine; these are—*Dicrocoelium lanceatum*, of which the normal host is the sheep; *Echinostomum malayanum*, from the Malay States; *E. ilocanum*, from the Philippines; *Artysctenostomum sufartyfex* (which is probably identical with *E. malayanum*), from Assam.



Fig. 227.—*Eriocheir japonicum*, ♂. Quarter nat. size. (Partly after Alcock.)

SCHISTOSOMIDÆ

The trematodes belonging to the genus *Schistosoma* are distinguishable from all other distomes by the structure of the intestinal canal, which, after primary bifurcation, fuses to form a single canal in the posterior portion of the body. These trematodes are unisexual—that is, the sexes are distinct and separate; furthermore, Laurer's canal, which is present in all the other genera we have considered, is absent in these parasites. The male is invariably bigger than the female, which is carried in a ventral expansion known as the *gynæcophoric canal*. The egg is non-operculated. Various species have been recognized in monkeys, cattle, and sheep. Three species infect man, viz. *S. hæmatobium*, *S. mansoni*, and *S. japonicum*.

SCHISTOSOMA HÆMATOBIUM (Bilharz, 1852) Weinland, 1858

Habitat.—This parasite (Fig. 228) is found in the venous system of man, especially the mesenteric branches of the portal vein, the vesico-prostatic, the pubic and uterine plexuses, and the vesical veins; occasionally it may wander into the vena cava and into the pulmonary veins. As many as 300 have been found at autopsy, and in experimentally-infected monkeys they may be even more numerous; they appear to be especially abundant in the veins of the submucosa of the bladder.

Originally observed as a natural infection by Cobbold in a monkey, *Cercocæbus fuliginosus*, the parasite can, under experimental conditions, be conveyed to a number of animals—rats, mice, guinea-pigs, and monkeys.

Geographical distribution.—*S. hæmatobium* is confined for the most part to the continent of Africa. Endemic foci also exist in Cyprus, Palestine, Arabia, and Mesopotamia. It is recorded that after the South African War the infection was imported into Perth, Western Australia.

General observations.—The adult parasite is long-lived. The Editor has seen active cases of the disease of twenty years' standing, and others, e.g. Christopherson, have recorded still longer periods. The sexes live apart while young, but on reaching maturity the female enters the gynæcophoric canal of the male.

Features common to both sexes.—In both sexes the alimentary canal commences at the oral sucker, the ventral sucker, or acetabulum, being prehensile in function. The œsophagus presents two dilatations, and bifurcates just in front of the ventral sucker to form two intestinal cæca, which again unite about the centre of the body into a median trunk. The excretory system consists of two longitudinal canals which open posteriorly and somewhat dorsally by the excretory pore.

The nervous system is represented by an œsophageal ganglion and commissure, embracing the œsophagus, from which the longitudinal nerve-cords run to the posterior end of the body; these cords intercommunicate by means of lateral branches.

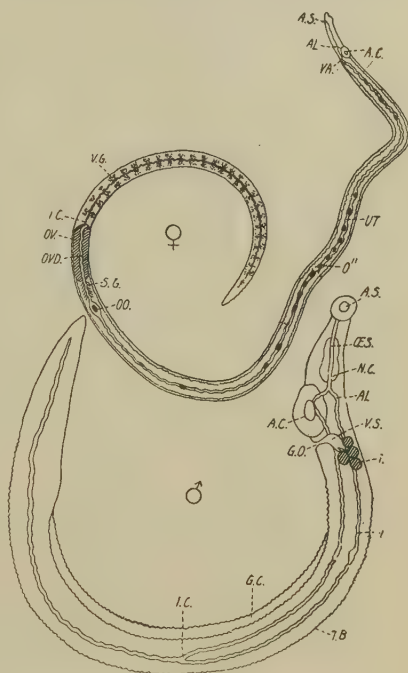


Fig. 228. — *Schistosoma hæmatobium*.
× 10. (Orig.)

A.C., Ventral sucker; AL, bifurcation of alimentary canal; A.S., anterior sucker; G.C., gynæcophoric canal; G.O., genital opening; I., intestine; I.C., union of intestinal cæca; N.C., nerve cord; O'', terminal-spined ovum; œs., œsophagus; oo., oötype; ov., ovary; ovd., oviduct; s.g., shell-gland; t., testes; T.B., tuberculations; ut., uterus; va., vagina; v.g., vitelline glands; v.s., vesicula seminalis.

The male is white, cylindroid, 1 to 1.5 cm. in length by 1 mm. in breadth, and it possesses an oral and a ventral sucker (of which the latter is the larger) placed close together. The oral sucker has the dorsal lip longer than the ventral. The cylindrical appearance of the worm is produced by the ventral infolding of the two sides of what would otherwise be a flat body. By this infolding a gynæcophoric canal is formed, in which the female can be partially enclosed. The outer surface of the body is closely beset with small cuticular prominences, especially on the dorsal surface. There are delicate spines on the suckers, and large tuberculations on the inner surface of the gynæcophoric canal.

The reproductive system consists of 4 to 5 testes, round in shape, and lying posterior and dorsal to the ventral sucker; from these a similar number of vasa efferentia unite to form a long vesicula seminalis, to open at the genital pore, in the median line, just posterior to the ventral sucker.

The female is rather darker in colour than the male, considerably longer (2 cm. by 0.25 mm. in breadth), and filiform; her middle portion is usually infolded in the gynæcophoric canal of the male, while her anterior and posterior portions remain free. Her body is smooth, except towards the posterior end and on the suckers, where papillæ abound. The reproductive system consists of an elongated oval ovary lying in the posterior half, in front of the union of the intestinal cæca. From the posterior pole of the ovary arises the oviduct, which on passing forwards is joined by the vitelline duct. The yolk-glands, or vitellaria, occupy the posterior part of the body.

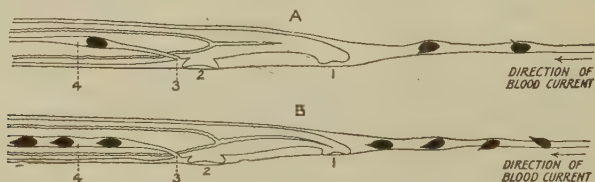


Fig. 229.—Diagram representing deposition of eggs by (A) *S. mansoni* and (B) *S. haematobium* in blood-vessels, and their passage to exterior. (Orig.)

1, Anterior sucker; 2, posterior sucker; 3, vaginal orifice; 4, uterus with contained eggs.

The shell-gland opens into the oviduct, which on passing forwards becomes the uterus. The genital opening is median, and situated just posterior to the ventral sucker. The anterior portion of the uterus contains several terminal-spined eggs. The genital openings of the sexes face each other, and are placed immediately posterior to the ventral sucker.

The egg.—On microscopical examination, the uterus of the female is found to contain 20–30 eggs of a peculiar and characteristic shape. They are oval, each egg on an average measuring about 150 μ in length by 60 μ in breadth. One end of the egg is provided with a short, stout, and very definite spine. (Plate XXXV, II, facing p. 874.)

The exact nature of the process by which the eggs leave the body of the human host has been explained by Fairley and the Editor from observations upon experimentally-infected monkeys whose mesentery had been exposed under anæsthesia. The paired worms travel against the blood-stream to the furthestmost possible point, where the female leaves her partner, and, being of a smaller diameter, is able by means of her suckers to progress until she

stretches the smaller venules to their uttermost. The eggs are now deposited with their spines directed posteriorly. The female then withdraws so that the egg she has deposited lies a little in front of the anterior sucker. The process is then repeated. When, after the deposition of an egg, the worm retires, the vein contracts to its original dimensions, embracing the egg, and the returning blood drives the spine into the wall of the vein. (Fig. 229.)

In a large proportion of cases, much more frequently than was formerly thought to be the case, the characteristic eggs of *S. hæmatobium* may be found in the fæces (Fairley), though it has not yet been proved that they are capable of forming the intestinal papillomata so characteristic of *S. mansoni* infections (see p. 524). Chesterman has reported from the Congo a much-elongated variety of terminal-spined egg which occurs in the fæces only, and not in the urine.

The free embryo or miracidium (Fig. 230).—In newly-voided urine the egg presents a somewhat brownish appearance, and generally contains a ciliated embryo, which escapes through a transverse rupture in the shell, caused by osmosis on coming into contact with

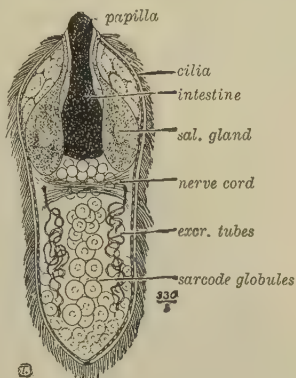


Fig. 230.—*Schistosoma hæmatobium* miracidium. (After Looss.)



Fig. 231.—Fresh-water molluscs. Nat. size. (Orig.)

1. *Bullinus contortus*; 2. *B. dybowskii*; 3. *B. innesi*; 4. *B. africanus*—all intermediary hosts of *S. hæmatobium*; 5. *Physa subopaca*, a sinistral snail apt to be mistaken for *Bullinus*; 6. *Lymnaea laurenti*, a dextral snail.

water. It then swims about, but, unless supplied with fresh water, perishes within a period of twenty-four hours. While swimming, the body of the miracidium undergoes many changes of shape. It moves by means of the cilia which, with the exception of the minute papillary beak, thickly cover the entire body. On careful examination, a primitive intestine may be traced from the anterior papilla; on each side of this, two unicellular salivary, or cephalic, glands can be made out,



Fig. 232.—Section of digestive gland of *Planorbis boissyi*, showing formation of sporocysts and cercariæ.

(Orig., from "Parasitology," Vol. XII, No. 1.)

with ducts opening into the mouth. The bulk of the embryo is occupied by a number of germ-cells, the posterior part by excretory tubules connected with four large flame-cells. The nervous system is represented by an oval, irregular mass lying in the centre of the body. According to Leiper and Ashworth's observations, the cuticle of the miracidium is composed of a number of polygonal epithelial cells. The body is divided transversely into three zones, united by six or seven longitudinal strands.

According to Dye, the miracidia of *S. hæmatobium* hatch more rapidly

and travel farther before entering their intermediate host than do those of *S. mansoni*.

Life-history.—The miracidium is attracted by the appropriate species of mollusc: in Egypt, by *Bullinus dybowski*, *B. innesi*, and *B. contortus*; in S. Africa, by *B. africanus*. (Fig. 231.) In Portugal, according to Bettencourt and Borges, development takes place in a planorbis, *P. dufourii* [*P. corneus* (L.) var. *metidjensis* (Forbes)]; in Northern Nyasaland, apparently, in *Melania nodocincta* (Dye).

The miracidium penetrates the soft part of the mollusc, usually boring its way through the antennæ. The cilia are then cast off, and in the liver, or digestive gland, the miracidium develops into an elongated sac-like body called a sporocyst, in the interior of which daughter-sporocysts form. These latter multiply to such an extent that the entire liver becomes permeated with the long, delicate, transparent, tube-like bodies. Presently numerous bifid-tailed cercariæ develop within the sporocysts (Fig. 232), and, on maturing, escape spontaneously into the surrounding water. The cycle from miracidium to cercaria under suitable conditions of temperature takes fourteen days to complete. Opportunity occurring, the now free cercariæ penetrate the skin of some suitable vertebrate—man, mouse, rat, monkey—dropping their tails in the process. (Fig. 240, 2.) Entering lymphatics or blood-vessels, they proceed to the liver of the definitive host, and in about six weeks attain sexual maturity and produce terminal-spined eggs. To obtain these results in the laboratory, all that is necessary is to place the living experimental vertebrate, or a part—tail, limb, etc.—of such animal, in water into which cercariæ have escaped from the snail, care being taken that the dose of cercariæ is not too large, as in such case the excessive invasion of the liver may prove rapidly fatal. In man, as well as in experimental animals, the presence of numerous examples of this parasite in the liver causes a heavy deposition of dark pigment in the interstitial cells.

Snail hosts.—The intermediary hosts, fresh-water snails of the genus *Bullinus*, have distinctive characters, and the opening of the shell is sinistral (Fig. 231). Annandale considers that all three species, *B. contortus*, *dybowski*, and *innesi*, are really varieties of *Bullinus truncatus* (Audouin, 1809), which is a synonym of *Bullinus contortus* (Michaud, 1831) (Fig. 231). The synonym of *B. africanus* is *Physopsis africana*. In Sierra Leone the species is *Bullinus globosus*, and, according to Porter in S. Africa, *Planorbis pfeifferi* and *Limnæa natalensis*.

SCHISTOSOMA MANSONI Sambon, 1907

Habitat.—In man the habitat of this trematode is the inferior and superior mesenteric veins, the hæmorrhoidal plexus, and the portal system. The schistosomes may best be obtained at autopsy by squeezing out all the venous blood from the liver against the side of a glass vessel, when they will adhere to the side of the glass, and can be picked off.

Geographical distribution.—This fluke is generally distributed throughout Africa, being abundant in Egypt, the Congo, and French West Africa. It is common in the South American continent—in Brazil, Venezuela, and Dutch Guiana, and in the Antilles, especially Antigua. It is thought that the extension of rectal schistosomiasis to the New World was due to the exportation of slaves from West Africa.

Male.—Length, 1-1.2 cm. The body behind the ventral sucker is clothed with wart-like tuberculations considerably larger and more pro-

nounced than in *S. hæmatobium*. The intestinal canal bifurcates at the level of the ventral sucker, but the intestinal cæca unite early in the anterior half of the body to form a long, single intestinal tract. The genital system consists of eight or nine small testes, with as many vasa efferentia opening into the vesicula seminalis. (Fig. 233.)

Female.—Length, 1.2–1.6 cm. As in the male, the intestinal æca unite in the anterior half of the worm.

Genital system.—The ovary lies in the anterior half of the body, in front of the union of the intestinal cæca, and in consequence the uterus is very short and contains a few lateral-spined eggs, or more generally one, with spine directed posteriorly. The yolk-glands occupy about two-thirds of the body at its posterior end. The eggs (Plate XXXV, 12, facing p. 874) are $150\ \mu$ long by $60\ \mu$ in breadth, on the average; the lateral spine itself measures $20\ \mu$

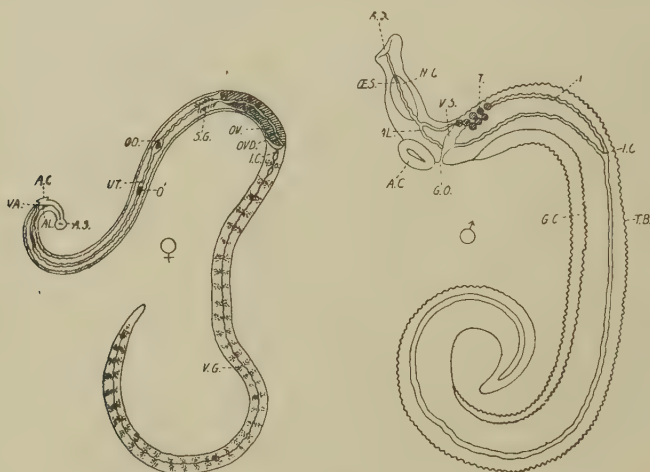


Fig. 233.—*Schistosoma mansoni*. $\times 10$. (Orig.)
(For lettering, see inscription to Fig. 228; o', lateral-spined egg.)

The miracidium is very similar to that of *S. hæmatobium*.

Life-history.—Except that the species of intermediary host concerned are different, this is identical with that of *S. hæmatobium* (p. 727). In the space of 10–15 minutes the miracidium penetrates into the tentacles of the mollusc, and produces thereby a swelling by which the infected snails can be recognized. Within three or four days the miracidium becomes a sporocyst, which on the fifth or sixth day gives rise to daughter-sporocysts, and these in turn migrate on the twentieth day to the liver. The cercariæ themselves are produced by the daughter-sporocysts (Lutz).

The cercaria differs slightly in measurements from that of *S. hæmatobium*. The main points of differentiation appear to be its slightly smaller size, the shorter furci, and especially the two large periacetabular glands. (Fig. 240, 1.)

After penetration of the host the trematodes take about six weeks to reach maturity. The females lay their eggs in the portal system, and eventu-

ally they are excreted by passing through the intestinal mucosa into the fæces, and by this means escape to the exterior.

Should the fæces be diarrhœic, the escape of the miracidium from the egg may even take place in the interior of the gut. The miracidia are said to be attracted by light, and to escape from the fæces in this manner.

In Egypt and the Sudan the intermediary host of *S. mansoni* is *Planorbis boissyi* (*P. sudanicus*, *P. pfeifferi*); in Nyasaland, *P. neosudanicus*; in Brazil, *P. olivaceus* and *P. centrimetralis*; and in Venezuela and the Antilles, *P. guadeloupensis*. (Fig. 234, c.) According to Porter, in South Africa *Bullinus africanus* can act as a host.

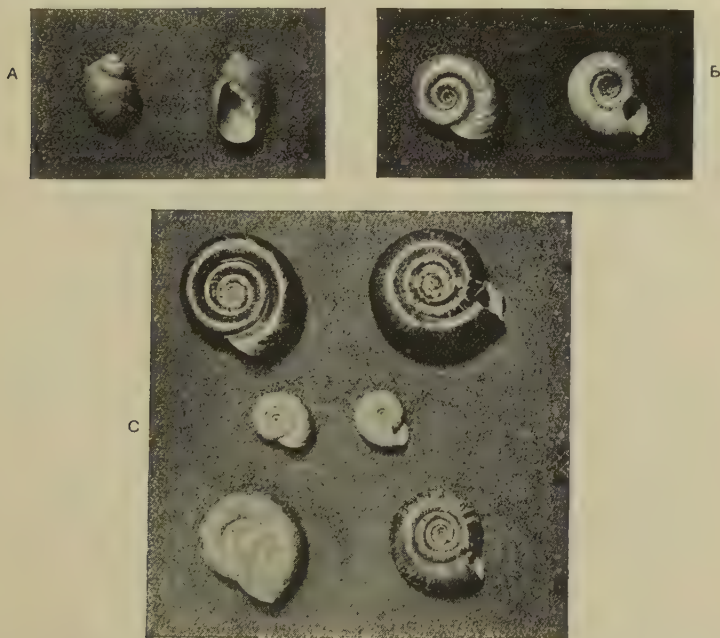


Fig. 234.—Carriers of *Schistosoma hæmatobium* and of *S. mansoni* in Egypt, South America, and West Indies. (After Leiper.)

A, *Bullinus contortus* (nat. size). B, *Planorbis boissyi* (nat. size). C, *P. olivaceus*; *P. boissyi*; *P. guadeloupensis* (two-thirds nat. size).

SCHISTOSOMA JAPONICUM (Katurada, 1904)

Habitat.—The habitat of *S. japonicum* in the human body is similar to that of *S. mansoni*. The adults of this species inhabit principally the veins of the large intestine, but they have been found also in the gastric, superior mesenteric, splenic, and cardiac veins. They occur as a natural infection in man, cat, pig, dog, and cattle (*Bos sinicus*), and under experimental conditions can be transmitted to monkeys, rabbits, mice, rats, and guinea-pigs. Large numbers have been found in man at autopsy, and a count of 20,000 has been recorded from an experimentally-infected horse.

Geographical distribution.—The parasite occurs commonly in Japan, China, Upper Burmah (Shan States), and the southern Philippine Islands, in curiously restricted endemic foci, due to the local distribution of the intermediary molluscan host.

Features common to both sexes.—This schistosome differs from the other two species mainly in its smaller size and the absence of tuberculations on the integument. (Fig. 235.)

The suckers are placed close together at the anterior extremity of the body; the acetabulum, or ventral sucker, is distinctly pedunculated or funnel-shaped; the suckers and the ventral surface of the body in the male are provided with minute spines. Both suckers are relatively larger than those of *S. hæmatobium*. The oesophagus is provided with two bulbs; the bifurcation of the alimentary canal takes place, as in *S. mansoni*, at the level of the ventral sucker, but the union of the intestinal cæca is effected more posteriorly, the united gut occupying one-quarter to one-fifth of the total body-length. The excretory system consists of two longitudinal canals which open dorsally by the excretory pore.

The male is 9–12 mm. in length by 0.5 to 1 mm. in breadth. The genital system consists of 6–8 elliptically-shaped testes, situated dorsally to the acetabulum. The vasa efferentia join to form a common duct opening directly posterior to it, while there is also a large seminal vesicle. The posterior portion of the body widens out, the sides overlapping one another far more extensively than in the two preceding species.¹

The female is 12–15 mm. in length by 0.3 mm. in breadth. The ovary is situated in the middle of the body, and the intestinal cæca unite immediately behind it. The well-developed yolk-glands extend almost to the posterior extremity. The uterus is well developed and occupies the anterior portion of the body; it may contain 50 or more eggs.

The eggs are oval, and are for practical purposes spineless; when seen in the fæces they measure 60–80 μ in length by 40–60 μ in breadth; on careful examination they are found to be provided with what may pass for a rudimentary lateral spine, in the form of a minute and easily-overlooked papilla like the excrescence in a cup-like depression of the shell. (Plate XXXV, 13, facing p. 874.) When measured in the uterus of the female, the eggs are considerably smaller and are about 67 μ by 50 μ (Faust and Meleney).

Probably the eggs are extruded from the blood-vessels in the same manner as has been described in the other species; they are found

¹ Great variation is to be noted in the measurements given by different authorities. Katsurada has reported both male and female up to a length of 20 mm.

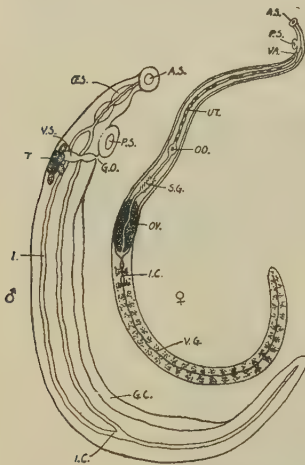


Fig. 235.—*Schistosoma japonicum*, male and female. $\times 10$.

A.S., anterior suckers; G.C., gynæcophoric canal; G.O., genital opening; I., intestine; I.C., union of intestinal cæca; O.S., oesophagus; O.O., oötype; O.V., ovary; P.S., posterior sucker; S.G., shell-gland; T., testes; V.A., vagina; V.G., vitelline glands; V.S., vesicula seminalis.

chiefly in the walls of the intestine, the liver, pancreas, and mesenteric glands.

The eggs are discharged in the fæces of the vertebrate host and, when carried into water, hatch into a ciliated miracidium. The morphology of this differs little from a similar stage of *S. hæmatobium* and *S. mansoni*, but the cephalic glands, according to Cort, are smaller.

DIFFERENTIAL TABLE OF THE HUMAN SCHISTOSOMES

ADULTS.	<i>S. hæmatobium</i> .	<i>S. mansoni</i> .	<i>S. japonicum</i> .
MALE	Finely tuberculated. Testes large, 4 in number.	Grossly tuberculated. Testes small, 8 in number.	Non-tuberculated. Testes elliptical, 8 in number.
FEMALE ..	Uterus contains large numbers of terminal-spined eggs. Lateral branches of intestinal canal unite in posterior third.	Uterus contains 1-3 lateral-spined eggs. Lateral branches of intestinal canal unite in anterior half.	Well-developed uterus occupies anterior portion of body, contains up to 300 eggs with knob in place of spine.
EGGS	150 μ long. 60 μ broad. Terminal spine.	150 μ long. 60 μ broad. Lateral spine.	80 μ long. 65 μ broad. Lateral knob.
PASSAGE OF EGG TO EXTERIOR	Urine, less frequently fæces.	Fæces, rarely urine.	Fæces only.
INTERMEDIARY HOSTS	<i>Bullinus contortus</i> (Egypt). <i>B. dybowskii</i> (Egypt). <i>B. innesi</i> (Egypt and Sudan). <i>B. truncatus</i> (Palestine—Jaffa). <i>B. globosus</i> (<i>Physopsis globosa</i>) (Sierra Leone). <i>B. africanus</i> (<i>Physopsis africana</i>) (Natal). <i>Planorbis pfeifferi</i> (S. Africa). <i>Planorbis corneus</i> var. <i>metidjensis</i> (Portugal). <i>Melania nodocincta</i> (Nyasaland). <i>Limnea natalensis</i> (Natal; rarely).	<i>Planorbis boissyi</i> (Egypt). <i>P. sudanicus</i> (Sudan). <i>P. neosudanicus</i> (Nyasaland). <i>P. pfeifferi</i> (S. Africa). <i>P. olivaceus</i> (Brazil and Dutch Guiana). <i>P. centrimetralis</i> (Brazil). <i>P. guadeloupensis</i> (Venezuela and Antigua). <i>Bullinus africanus</i> (<i>Physopsis africana</i>) (Natal).	<i>Oncomelania nosophora</i> (Japan and China). <i>Oncomelania hupensis</i> (Yangtse Valley). <i>Oncomelania formosana</i> (Formosa).

Life-history.—This takes place in a manner similar to the preceding. After shedding its cilia the miracidium becomes a sporocyst in the liver and hermaphrodite gland of a fresh-water mollusc, *Oncomelania nosophora*, and allied species. The sporocysts are delicate, elongated, and finger-like; in their interior cercariæ develop. Each sporocyst is capable of giving rise to 50 or more daughter-sporocysts.

The cercariæ, which develop in the snail sixty days after infection, are similar to those already described, but are smaller, being 0.32 mm. in length by 0.04 mm. in breadth. (Fig. 241.)

The body of the cercaria is covered with minute spines. The oral sucker

is greatly developed, occupying the anterior third of the body, and is on its free margin provided with a number of minute papillæ; there are five pairs of periacetabular glands connecting with the oval sucker by means of ducts. There is also a single pyriform gland in the head, dorsal to the digestive tube. Narabayashi states that the cercariæ are photophobic, and unable to survive a temperature above 50° C. or below 2° C. When fully formed the cercariæ escape into water and, opportunity presenting, penetrate the skin of some appropriate vertebrate, in which they attain maturity. The minute flukes can be found in the liver, measuring 150 μ . On the thirtieth day copulation takes place, and in the fifth week eggs appear in the faeces. The cercariæ reach the lungs through the pulmonary arteries, and travel via the mesenteric arteries, mesenteric veins, and portal vein to the liver (Meleney and Faust).

Snail hosts.—Considerable confusion has existed with regard to the correct nomenclature of the snail hosts of *S. japonicum* in China and Japan.



Fig. 236.—Molluscan hosts of *Schistosoma japonicum*. $\times 6$.
(After Faust and Meleney, "Amer. Journ. of Hyg.")

A, *Oncomelania nosophora*. B, *Oncomelania formosana*. C, *Oncomelania hupensis*.

The genus has been variously named *Katayama* Robson, 1915; *Hypsobia* Robson, 1921; *Blanfordia* Pilsbury, 1915; and *Hemibia* Heude, 1889.

Annandale, in a recent authoritative statement, has concluded that all the known and suspected hosts belong to a single genus, of which the correct name is *Oncomelania* Gredler, 1881, but that the genus may be divided into two sections, *Katayamæ* and *Hemibiæ* (gasteropod snails belonging to the Family Hydrobiidæ).

The shells in both sections are long and narrow, with many whorls, and with the breadth increasing gradually from the apex downwards; usually they are 5–12 mm. in height. The basal whorl is never much broader than the one above it, and the apex of the shell, when not worn away, is sharp. The mouth of the shell is ovate, broadly rounded below. The outer lip is sharp, but on the external surface there is a coarse ridge. The operculum

is very thin and transparent, of ovate outline, with a small spiral figure on the inner side. (Figs. 236, 237.)

In the section *Hemibia* there are stout, convex, smooth, vertical ribs on the surface of the shell, while in the *Katayama* these are replaced by faint lines.

All the species which are potential hosts of *S. japonicum* in China, Japan, and Formosa live in damp places, but not in water, and bury themselves in earth when climatic conditions are unfavourable.

There is not much difficulty in recognizing this genus in China, but in Japan it is closely simulated by the genus *Blanfordia*, whose shell is very similar in every respect, but the number of whorls is smaller and the contained animal differs considerably in having a proboscis-like snout. The following species are now recognized as carriers of *S. japonicum*:

1. *Oncomelania nosophora* (Robson, 1915). The only known carrier in Japan, and probably the main one in China. (Fig. 236, A.)

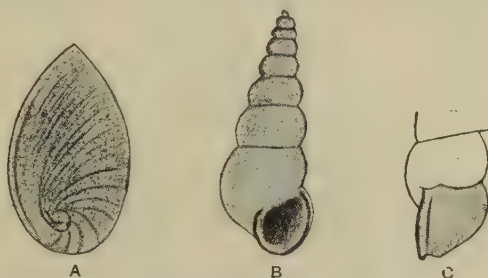


Fig. 237.—Operculum and shell of *Oncomelania nosophora*. (After Robson.)

A, Operculum, $\times 12$, diagrammatic to show scheme of coiling. B, Oral aspect of shell, $\times 4$.
C, Lateral aspect of shell, showing labial swelling, $\times 4$.

2. *Oncomelania formosana* (Pilsbury and Hirase, 1905), distinguished from the preceding by its relatively shorter and broader shell. It appears to be the main carrier in southern Formosa (Yokagawa). (Fig. 236, B.)

3. *Oncomelania hupensis* (Gredler, 1881). This species has been discovered to be the main carrier of infection in Kiangsu, China, and closely resembles the last-named species. It is found on the banks of the hill-streams and of the canals of the plains. (Fig. 236, C.)

PARAMPHISTOMIDÆ

GASTRODISCOIDES HOMINIS (Lewis and MacConnell, 1876)

Habitat.—*G. hominis* is found in the cæcum and large intestine.

Geographical distribution.—Malay States, Assam, India, Cochin China. Cases have been reported from other parts of the world, e.g. British Guiana, in immigrants from endemic areas.

Characters.—The normal host of *G. hominis* in Cochin China is the pig; it has also been found in a Napu mouse-deer from the Malay States. Fresh specimens of this parasite are reddish in colour. In the living state the body is very contractile and can be elongated to a length of 1 cm. Preserved specimens measure 5–7 mm. in length by 3–4 mm. in breadth at their widest point. The body is divided into an anterior conical and posterior discoidal portion, which forms a flattened, ventrally concave disc. On the anterior

conical portion, in the midline, 2.5 mm. from the oral sucker, is a prominent genital papilla in which is situated the common genital pore. The acetabulum is situated ventrally in the caudal portion of the body. It is circular, and measures 2 mm. in diameter. The cuticle is smooth; no spines are present. (Fig. 238.)

The *alimentary canal* consists of a pharynx with two pear-shaped pharyngeal pouches. The oesophagus is 1 mm. long, and ends in a muscular bulb; at this point the bifurcation of the intestine takes place, and both cæca run back as far as the anterior edge of the acetabulum.

The *male genital organs* consist of two lobulated testes which lie diagonally

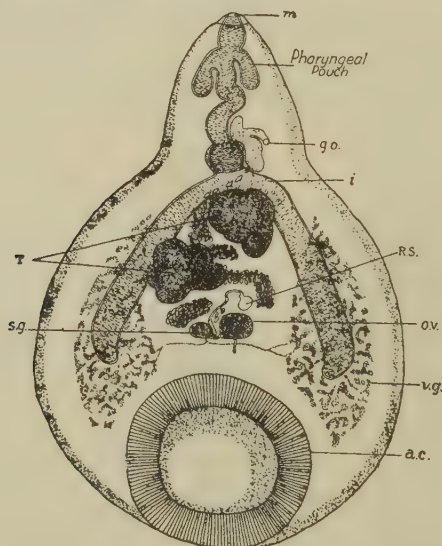


Fig. 238.—*Gastrodiscoides hominis*. $\times 15$. (After Khalil, "Proc. Roy. Soc. Med.")

t., Testes; s.g., shell-gland; m., mouth; g.o., genital opening; i., intestine; r.s., receptaculum seminis; ov., ovary; v.g., vitelline glands; a.c., acetabulum.

in the space between the intestinal cæca. A seminal vesicle is present, but there is no cirrus.

Female genital organs.—The ovary lies in the midline of the body posterior to the testes; it is ovoid in shape. The shell-gland lies at the side of the ovary, while the receptaculum seminis lies in front of it. The uterus is short, and lies for the most part in the space between the two testes. Laurer's canal is present.

The vitellaria lie in the middle-third of the body, and surround the posterior halves of the intestinal cæca.

The eggs are 152 μ in length, with a maximum diameter of 60 μ ; an operculum is present.

The life-history is unknown.

Pathogenesis and treatment.—Very little is known regarding the effect of this parasite on man, but it can easily be expelled from the intestinal canal by thymol treatment.

One other member of the Paramphistomidæ has been recorded, once only, from man, *Watsonius watsoni*. Large numbers of this fluke were found in 1904 in the upper part of the jejunum of a negro patient from German West Africa. The normal host is probably a monkey. It has been recorded from *Cercopithecus callitrichus* in French Guinea.

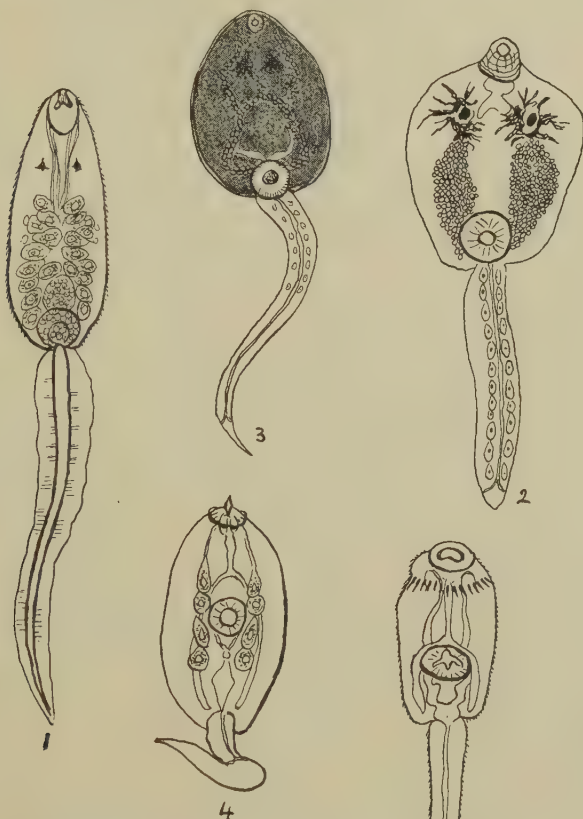


Fig. 239.—Examples of cercariæ. $\times 110$; No. 3, $\times 30$. (After Faust, "Journ. Parasitol.," by permission; 3, after Looss.)

- 1, Monostome (*C. pleurolophocerca*). 2, Amphistome with eyespots (*C. frondosa*). 3, Pigmented amphistome (cercaria of *A. conicum*). 4, Distome xiphidio-cercaria (anterior end with stylet). 5, Distome echinostome (anterior end with collar of spines).

CERCARIÆ

The frequent occurrence of larval trematodes, of which the adults are unknown, in various fresh-water molluscs has rendered it necessary to classify them on a morphological basis. (Fig. 239.)

The commoner forms may be classified as follows:—

1. MONOSTOME CERCARIÆ. Ventral sucker lacking.
2. AMPHISTOME CERCARIÆ. Ventral sucker at posterior end of body.
3. DISTOME CERCARIÆ. Ventral sucker situated towards the middle of the body. The cercariæ of most of the flukes occurring in man fall into this class, which contains many subdivisions, among which are—

- (a) *Leptocercous cercariæ*, with straight slender tails;
- (b) *Microcercous cercariæ*, with short tails;
- (c) *Echinostome cercariæ*, with a circle of spines surrounding the anterior sucker;
- (d) *Furcocercous*, or *fork-tailed cercariæ*, so characteristic of the schistosome group.
- (e) *Xiphidio-cercariæ*, with a simple tail, and bearing a stylet in the oral sucker,

There are two rarer forms, as follows:

4. GASTEROSTOME CERCARIÆ, with the mouth opening in the middle of the ventral surface.

5. LOPHOCERCARIÆ, with longitudinal cuticular projections running along each side of the body.

Furcocercous cercariæ, besides those of the human schistosomes, have been found in snails of the genera *Bullinus*, *Planorbis*, and *Limnæa* in Egypt, India, South Africa, Europe, and North America. The majority of these can be differentiated from the schistosome cercariæ of man by their measurements, morphological distinctions, the presence of a pharynx or of eyespots, or by the cuticular expansion of the tail. Some have been found in operculated snails such as *Oncomelania*, *Cleopatra*, and *Melania*. Therefore the presence of furcocercous cercariæ in fresh-water snails, even of the appropriate genera, does not necessarily indicate the presence of human schistosomiasis in the district. (Fig. 240.)

In India, where the disease is not endemic, fork-tailed cercariæ from *Planorbis exustus* have been found to be intermediary stages of *Schistosoma spindalis* of the goat; while Sewell has described a cercaria (*Cercaria indica* No. XXX) non-pathogenic to man, having apparently a morphology and measurements similar to those of *S. japonicum*, from *P. exustus*, and from *Limnæa amygdalum*.

Cort has observed that the number of cercariæ which escape from infected snails is very large; that in doing so they may observe a certain periodicity, and that in some species they escape during the daytime, in others at night.

The following is a description of the cercaria of *S. mansoni* and of *S. japonicum*, which may be taken as types of the schistosome cercariæ (see Fig. 240).

Structure of the schistosome cercariæ.—The cercaria consists of a body and an elongated forked tail (Fig. 241), and measures about 0.48 mm. in total length. The outer cuticle of the body and tail is beset with microscopic spines. The body contains an anterior or oral and a median or ventral sucker; the former is the larger of the two, and occupies the anterior third of the body. The central part of the sucker is occupied by oral glands; in the midline runs the œsophagus, and on either side the ducts of the conspicuous periacetabular glands, which open by small retractile papillæ surrounding the mouth. The contraction of the circular muscles compresses the ducts and expresses the secretion, in-

dicating the method by which the cercaria burrows into the tissues of its definitive host. The mouth-opening itself is small, oval in shape, and

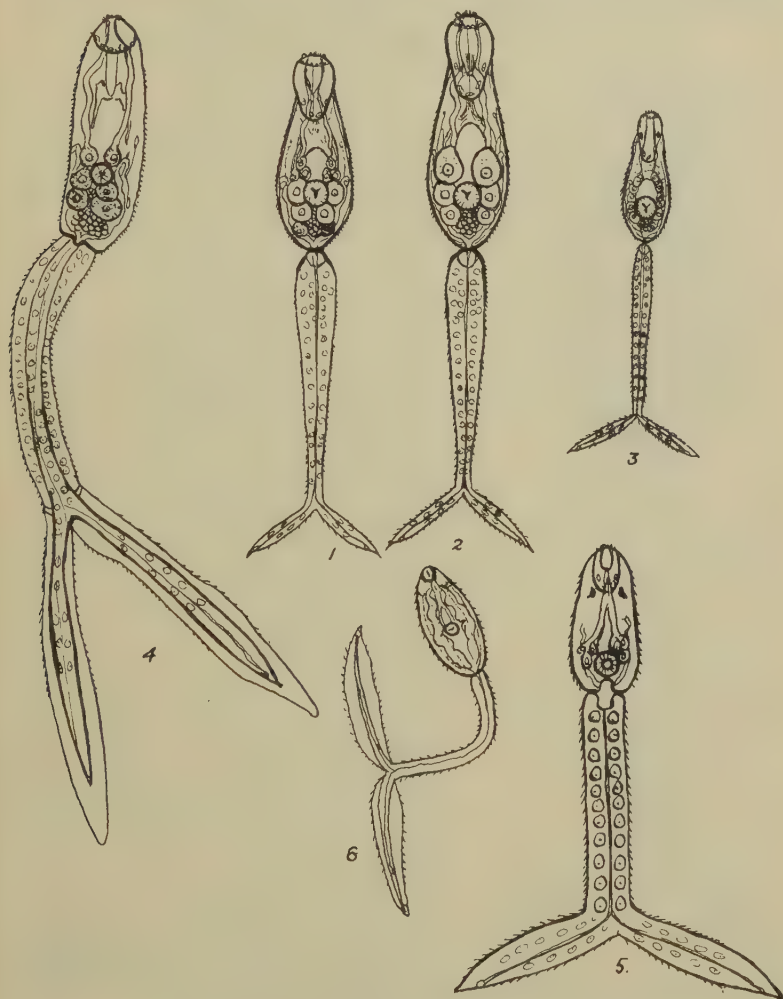


Fig. 240.—Fork-tailed cercariæ. $\times 100$

(Partly original ; partly after Leiper, Faust, and Looss.)

1, *S. mansoni* cercaria. 2, *S. hæmatobium* cercaria. 3, *S. japonicum* cercaria. 4, *Cercaria gladii*. 5, *C. minor*. 6, *C. vivax*. 4, 5 and 6 are typical furcocercous cercariæ which resemble in many ways the schistosome cercariæ.

placed on the anterior surface, while the œsophagus begins at its lower pole. The ventral sucker is smaller but more muscular than the oral ; its cuticle is covered with small spines pointing to the periphery.

The periacetabular glands are three in number, and consist of large clear cells with acidophil protoplasm and conspicuous nuclei.

The primitive nerve-ganglion lies anterior to the ventral sucker; posterior to the acetabulum is a mulberry-like mass of round cells representing the primitive genital centre.

The excretory system (Cort) consists of six pairs of flame-cells arranged along the margins of the body, and from these arise canals that form collecting tubules of a greater calibre which, running both forwards and backwards, meet at the posterior end of the body, and the duct is continued through the tail.

The cercariæ of the three human species differ morphologically in minor respects, as shown in the table on p. 739.

In water the cercariæ swim with ease, movement being accomplished by bending from side to side with lashing movements of the tail, which usually precedes the body, and when the surface of the water is reached the furci are stretched out at right angles so that the body and tail hang vertically downwards. When the water is disturbed the cercariæ immediately become active. Kept in a vessel or a tank, they adhere by means of the ventral sucker to the sides of the glass. In fixing on to an object the cercaria elongates itself to nearly double its normal length. Movement is effected by releasing the ventral sucker, contracting the body, and at the same time affixing by means of the oral sucker; the larva can then advance considerably. The lips of the oral sucker can be extended or retracted to a great extent; this probably serves a useful purpose and assists it in entering the skin.

After their emission from the snail the cercariæ can survive for 24-36 hours, but they require an abundant supply of oxygen; they are said to be photophobic.

When it comes into contact with the skin or mucous membrane of a suitable intermediary host the cercaria casts its tail, pierces the epithelium, and gains entrance into the deeper tissues. Warmth appears to be the main tactic factor. On entering the host the larva is known as a *schistosomulum*, and loses its glandular

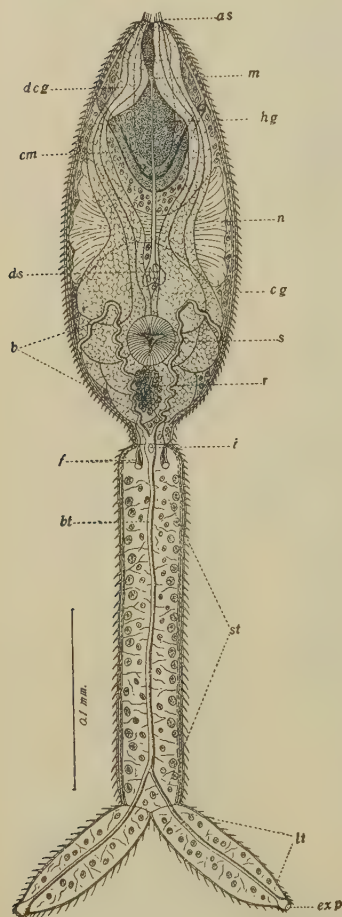


Fig. 241.—Cercaria of *Schistosoma japonicum*, ventral view. $\times 240$.

(After Cort, "Univ. of California Publications in Zoology.")

as, Anterior spines; b, excretory bladder; cg, cephalic glands; cm, circular muscles; dca, ducts of cephalic glands; ds, digestive system; exp, excretory pore; f, flame-cell; hg, head-gland; i, island in excretory bladder; lt, lobe of tail; m, mouth; n, nervous system; st, stem of tail; r, rudimentary genital cells; s, ventral sucker.

cephalic cells. After an incubation period of six weeks, mature females can be found in the portal vein with well-developed eggs in their uterine cavities.

MEASUREMENTS AND CHARACTERS OF SCHISTOSOME CERCARIÆ

	<i>S. hæmatobium.</i>	<i>S. mansoni.</i>	<i>S. japonicum.</i>
TOTAL LENGTH ..	0·52 mm.	0·514 mm.	0·33 mm.
BODY	0·24 mm. × 0·1 mm.	0·189 mm. × 0·73 mm.	0·12 mm. × 0·046 mm.
TAIL	0·20 mm. × 0·04 mm.	0·25 mm. × 0·043 mm.	0·15 mm. × 0·02 mm.
FURCI	0·08 mm.	0·075 mm.	0·06 mm.
OUTLINE ON LATERAL VIEW	Marked protrusion of ventral sucker.	No protrusion of ventral sucker.	Ventral sucker slightly protuberant.
SALIVARY-MUCIN GLANDS (after Faust)	Two pairs with large nuclei and granular acid protoplasm. Three pairs with baso- philic protoplasm.	Two pairs with large nuclei and granular acid protoplasm. Four pairs with baso- philic protoplasm.	Five pairs with baso- philic protoplasm.

CESTODA

The tapeworms are elongated and, as a rule, segmented Platyhelminthes of a white or yellow colour, devoid of mouth or of alimentary canal, but with organs situated at the anterior extremity, for attachment to the body of the definitive host. The whole body is called a *strobila*, and is composed of a head, or *scolex*, which carries the organs of attachment, and a colony of individual segments connected with each other and each capable of reproduction. The individual segments are known as *proglottides*. The scolex, which is separated from the proglottides by a narrow unsegmented neck, carries suckers, and sometimes hooks, which constitute the organs of attachment. The suckers may be (a) slit-like or false, in which case there are always two, or (b) cup-like and round, in which case there are always four.

It is possible to divide the cestoda occurring in man into two large orders upon the above characteristics :—

ORDER i.—The Pseudophyllidea. Those with the false or slit-like suckers.

ORDER ii.—The Cyclophyllidea. Those with cup-like and round suckers.

ORDER i.—PSEUDOPHYLLIDEA

Anatomy. *Proglottides*.—The interior of each proglottis consists of parenchymatous tissue, in which lie the various organs.

The *nervous system* consists of an anterior nerve-ring, from which spread two longitudinal cords, running throughout the entire length of the body parallel to the margins of the proglottides and giving off branches to the various structures in each segment.

The *excretory system* consists of a network of branched canals, originating in each instance from a flame-cell. Longitudinal excretory canals run through the strobila parallel to the nerves.

Reproductive system.—The male organs consist of numerous testes scattered throughout the lateral aspects of the body; from these as many vasa efferentia run inwards to form a vas deferens, which opens in the anterior

portion of the common genital pore, situated in the anterior part of the segment in the midline of the ventral surface. (Fig. 242, A.)

The female organs consist of two ovaries lying side by side in the posterior part of the segment; between these is situated the shell-gland. Leading from the posterior part of the common genital pore is a narrow vagina, the terminal portion of which is hollowed out to form a receptaculum seminis; this joins the oviduct as well as the collecting ducts from the vitellaria, which themselves lie on each side of the segment immediately in front of the shell-glands. The tubular uterus, which also commences at this point, occupies the central portion of each segment and passes forward to a birth-pore that is situated immediately posterior to the common genital pore. (Fig. 242, B.)

The eggs, which are thick-shelled and operculate at birth, contain an ovum and yolk-cells.



Fig. 242.—Mature segment of *Dibothriocephalus latus*. (After Sommer and Landois, in Brumpt's "Précis de Parasitologie.")

A, Dorsal, or male aspect. T., testes; v.d., vas deferens; v.g., vitelline glands.
B, Ventral, or female aspect. Cp., cirrus pouch; ov., ovary; s.g., shell-gland; ut., uterus;
va., vagina; v.g., vitelline glands.

DIBOTHRIOCEPHALUS LATUS (Linn., 1758)

Habitat.—The small intestine of man, dog, and cat.

Geographical distribution.—Europe—especially Sweden, Russia, Switzerland, and Roumania. Asia—Turkestan and Japan. Africa—Madagascar and Central African lakes.

Characters.—*D. latus* is greyish in colour, and may attain a length of 10 metres. Multiple infections are not infrequent. The scolex, which is 3 mm. in length, has no rostellum or hooklets, but is provided with two slit-like suckers, or longitudinal grooves, called bothria. The neck is thin, and the proglottides number 3,000–4,000.

This worm is remarkably long-lived, and has been observed in one individual for a period of 13 years. The mature segments are considerably broader than long. For anatomy, see general description at p. 739.

Life-history and pathogenesis (Fig. 243).—The eggs are brown in colour and operculated. They measure 70 μ in length by 45 μ in breadth. (Plate XXXV, 21, facing p. 874.) They occur in very large quantities in the fæces,

owing to the fact that every mature segment is giving birth to eggs simultaneously, and that none of the segments are being lost as is the case of the Cyclophyllidea. The life-history of *D. latus* was first worked out by Rosen and Janicki in 1918.

After developing for three weeks in water, a ciliated embryo or onchosphere (six-hooked) appears within the egg-shell. This escapes through the operculum and by means of its cilia swims about in the water as a free-living organism for several days; at this stage it measures 22–30 μ in diameter, and it is ingested by certain fresh-water crustacea, *Cyclops strenuus* and *Diaptomus*

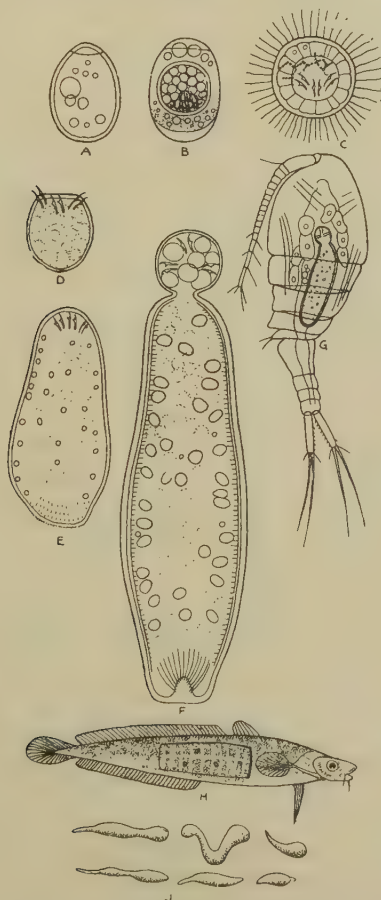


Fig. 243 — Evolutionary cycle of *Dibothriocephalus latus*. Drawn to different scales. (Partly after Brumpt.)

A, Egg of *D. latus*; B, hexacanth embryo; C, ciliated onchosphere or coracidium; D, E, F, development of larva, or proceroid, in *Cyclops*; G, proceroid in body-cavity of *Cyclops*; H, development of proceroids in fishes; I, proceroids of different shapes, ingested by man, dog, or cat.

gracilis, in the intestinal canal of which, within a period of two to three weeks, it is transformed into a *proceroid larva*, ovoid in form, with a terminal spherical appendix which carries the six embryonic hooks that were present in the onchosphere. The total length at this stage is 50–60 μ . No more than two onchospheres can develop in an individual cyclops; the latter is in turn swallowed as food by a fresh-water fish, which may be one of the following:

Europe: Pike. *Esox lucius*.
 Perch. *Perca fluviatilis*.
 Salmon. *Salmo umbla*.
 Trout. *Trutta vulgaris*.
 Lake trout. *Trutta lacustris*.
 Grayling. *Thymallus vulgaris*.

Japan: *Oncorhynchus perryi*.

Africa: Certain species of barbel.

On reaching the stomach of the fish, the proceroid larva penetrates its wall and after three or four days appears in the body-cavity and becomes encysted as a *plerocercoid larva* in the muscular and connective tissues of the flesh; it then measures 6 mm. in length. At this stage it develops characteristic cephalic grooves, nervous and excretory systems. On being ingested with raw roe (caviare), or insufficiently cooked fish, the plerocercoid develops, within a period of five or six weeks, into the adult *Dibothriocephalus* in the intestinal canal of man.

Pathogenesis.—The symptoms produced by *D. latus* are usually trifling; there is an early eosinophilia, and a severe anæmia has been known to ensue in certain cases.

DIPLOGONOPORUS

The only other genus of Pseudophyllidea occurring in man is *Diplogonoporus*. Two species have been described—*D. grandis* from Japan, and *D. brauni* from Roumania.

The normal host of *D. grandis* is the seal, and only two cases of infection have been observed in man. In *Diplogonoporus* the genital organs are symmetrically doubled in each segment.

LARVAL PSEUDOPHYLLIDEA OCCURRING IN MAN

DIBOTHRIOCEPHALUS MANSONI (Cobbold, 1883)

Geographical distribution.—Japan, China, East Africa, Australia, and British Guiana.

Sparganum mansonii is the plerocercoid stage of a member of the genus *Dibothriocephalus* which usually attains its adult stage in dogs and cats. Under normal conditions the plerocercoid stage is passed in a frog, *Rana nigromaculata*, or a snake, *Elaphe climacophora*, and the proceroid stage in a cyclops, *C. leuckarti*.

Man becomes infected by accidentally swallowing the proceroid stage in the cyclops while drinking. He thus takes the place of the frog or snake and becomes the second intermediary host.

Sparganum mansonii, as it was first named by Cobbold, was first described by Manson in 1882 in making the post-mortem examination of a Chinese in Amoy; since that date about 60 cases have been reported. The subsequent experiments which determined the life-history were first carried out by Yoshida, and afterwards confirmed by Okumura.

The measurements of sparganum, as originally given, are 8–36 cm. in length, 0.1–12 mm. in breadth, and 0.5–1.75 mm. in thickness. (Fig. 244.)

The body is flat, unsegmented, and transversely wrinkled. On the ventral

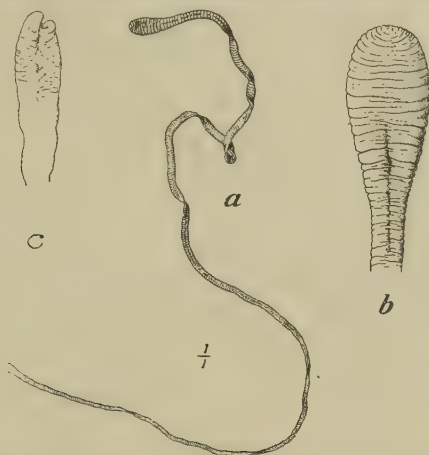


Fig. 244.—*Sparganum mansonii*, extracted from an abscess in a Masai.

(After Sambon.)

a, Natural size; b, anterior extremity; c, posterior extremity.

surface there is, as a rule, a longitudinal median groove. No sexual organs are present.

Pathogenesis.—In man the parasites may occur in practically any part of the body; they have been found in the neighbourhood of the kidneys and iliac fossæ, the pleural cavity and subcutaneous tissues. They have also been found in the urethra.

Ocular sparganosis.—Casaux and others have described this condition as frequently occurring in and about the Tonkin delta. The presence of the parasite in the orbit is characterized by pain, redness and œdema of the eyelids, with lacrymation and marked ptosis. The parasites have been found under the conjunctiva in Japan, and similar periocular swellings are reported from China.

SPARGANUM PROLIFERUM (Ijima, 1905)

This parasite, which is thought to be the larval stage of a pseudophyllid worm, has been found on two occasions encysted in the subcutaneous tissues, once in Japan and the other time in Florida.

The larvæ may be 3–12 mm. in length by 2.5 mm. in breadth. (Fig. 245.) The body contains calcareous corpuscles. Excretory

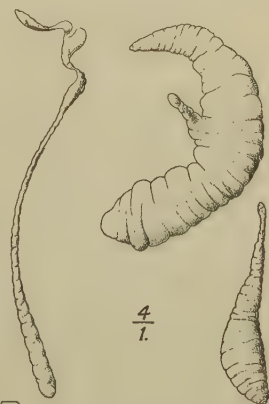


Fig. 245.—Different forms of *Sparganum proliferum*.

(After Ijima.)

canal and nerves are present. The parasites are usually contained in cysts, which can easily be enucleated.

In the cases reported, thousands of parasites were present in the subcutaneous tissue, intramuscular fasciæ, walls of the alimentary canal, mesentery, kidney, lung, heart, and brain. The prognosis of these cases is grave, as the larvæ are liable to become disseminated throughout the body.

ORDER ii.—THE CYCLOPHYLLIDEA

There are four main features in which the Cyclophyllidea differ from the Pseudophyllidea :

- (1) The head bears four cup-like suckers.
- (2) The genital pore, instead of opening ventrally, opens laterally in each segment.
- (3) There is no uterine opening or "birth-pore." The eggs are discharged by the bursting of the ripe segments, or proglottides, which become detached from the body of the worm and are passed in the fæces.
- (4) The egg is not operculated, and contains an onchosphere when discharged from the segment.

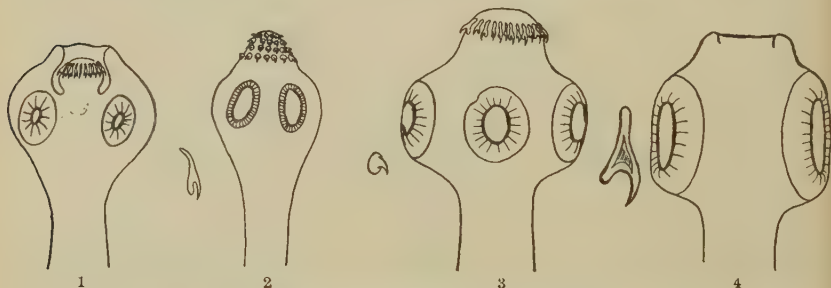


Fig. 246.—Heads of human cestodes, showing suckers and, when present, arrangement of hooklets. Diagrammatic.

1, *Hymenolepis nana* ; 2, *Dipylidium caninum* ; 3, *Taenia solium* ; 4, *Taenia saginata*.

Anatomy.—The cyclophyllid worms are composed of a head, neck, and immature, mature, and ripe segments.

The head carries four circular suckers and a rostellum which may, or may not, be armed with hooklets. (Fig. 246.)

The neck is slender, and varies in length according to the species.

The number of segments varies from a few (*Echinococcus granulosus*) to several thousands (*Taenia saginata*).

Throughout the strobila are scattered refractile bodies known as "chalk-bodies," which, when placed in weak acid, give off bubbles of carbon dioxide. These chalk bodies are extremely plentiful in the larval forms of tapeworm, and it is thought that they act protectively against the hydrochloric acid of the stomach, through which the larva has to pass on its way to the intestine.

Nervous system.—This commences as a ganglionic commissure in the head, from which lateral branches pass throughout the entire series of segments.

The **excretory system** consists of a number of "flame-cells" scattered throughout the parenchyma, from which small ducts lead into the longitudinal excretory canals ; these open in the posterior segment.

Reproductive system.—Each segment is a separate hermaphrodite individual. The male organs reach maturity before the female, thus exhibiting *protandry*. As the female organs develop, the male organs disappear, and finally, in the ripe segment, nothing but the gravid uterus remains.

Male organs consist of numerous testes which are scattered throughout the segment. Vasa efferentia from these join to form a vas deferens, which is connected with an exsertile cirrus opening laterally in the anterior portion of the common genital pore.

Female organs consist of two ovaries, which usually lie side by side in the posterior half of the segment; from these arise two oviducts which, after uniting opposite the receptaculum seminis, pass on as a single tube. This receives the vitelline duct, and, continuing through the shell-gland, becomes transformed into what is known as the uterus.

In connexion with the receptaculum seminis, and passing from it in the direction of the common genital pore, is a tube of fine calibre forming the vagina, used only for copulation.

The cyclophyllid egg is composite, and contains an ovum and yolk-cells; when it is passed, there are two shells, which vary in thickness according to the species; the inner (or *embryophore*) contains a six-hooked embryo, or *onchosphere*, while in the space between it and the outer shell (or *oötype*), yolk-cells are massed.

In certain species (e.g. *T. saginata*) the oötype is so delicate that it is not generally demonstrable in freshly-passed fæces, while in others (e.g. *Hymenolepis nana*) the oötype persists as a strong outer shell.

ADULT CYCLOPHYLLIDEA OCCURRING IN MAN

TÆNIIDÆ.

Tænia.

T. solium

T. saginata.

HYMENOLEPIDÆ.

Hymenolepis.

H. nana.

H. diminuta.

Dipylidium.

D. caninum (rare).

DAVAINEIDÆ.

Davainea.

D. madagascariensis (rare).

For illustrations of eggs of cestodes, see Plate XXXV.

TÆNIA SOLIUM (Linn., 1758)

Habitat.—Anterior third of small intestine. The specific name, *solium*, probably refers to the remarkable resemblance of the rostellum to the conventional figures of the sun.

Geographical distribution.—*T. solium* has a world-wide distribution coextensive with that of its intermediary host, the pig. For this reason it is unknown among Mohammedans, Jews, and other races that do not eat pork.

Characters.—*T. solium* generally attains a length of 2–3 metres, exceptionally 8 metres or more. The head, globular and roughly quadrangular, measures about 1 mm. in diameter. The rostrum is short, may be pigmented,

and bears a double row of 25–50 hooklets. (Fig. 246, 3.) The four suckers project slightly and are circular, each measuring $\frac{1}{2}$ mm. in diameter. The anterior proglottides are small, but broader than long; whereas the more mature are just the reverse of this—12 mm. long by 6 mm. broad. Each proglottis bears one marginal genital pore with thick lips; the situation of the pore alternates irregularly between the right and the left margin. The uterus lies in the median plane and bears 7–10 stout diverticula. (Fig. 247, A.) The eggs are globular or slightly oval, $31\text{--}56\mu$ in diameter, and have a vitelline membrane; inside the radially striated shell is a six-hooked onchosphere. (Plate XXXV, 16, facing p. 874.)

Life-history and pathogenesis.—The mature segments become detached, four or six at a time, and pass to the exterior with the faeces, where, by process of disintegration, the eggs are set free. They are then taken into

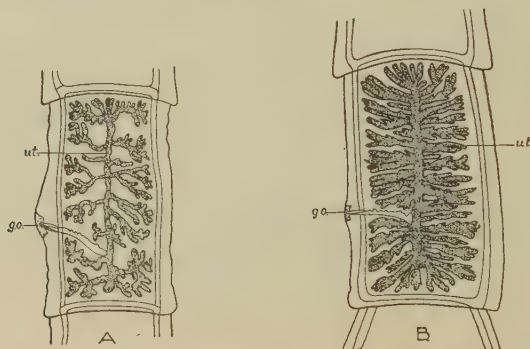


Fig. 247.—Segments of tapeworms. To show characteristic branching of uterus, as seen in mature segments.

A, *Tænia solium*. B, *Tænia saginata*.

ut., Uterus; g.o., genital opening.

(After R. Blanchard, in Brumpt's "Précis de Parasitologie.")

the alimentary tract of the intermediary host—in this case the pig—either in contaminated water or soiled food; man himself may exceptionally become infested in the same way. The onchosphere now passes through the gut-wall and, gaining the blood-stream, settles down in the muscular tissue, loses its hooks, and becomes a cysticercus 5–20 mm. long, generally known as *Cysticercus cellulosæ*, in which a small invaginated scolex and neck is produced resembling in miniature that of the adult tænia.

In man, however, the cysticercus may develop in any organ, especially the muscles of the tongue, neck, or ribs; less frequently in the liver, heart, lungs, or brain. A *Cysticercus cellulosæ* has been recorded in the human eye; in one case it is known to have persisted there for more than twenty years.

Pork-flesh infested with this cysticercus is known as "measly pork."

When the cysticercus is taken into the alimentary tract of man, or the definitive host, the bladder is dissolved by the gastric juices, and the scolex and neck is evaginated; it then passes into the small intestine, where the scolex fixes itself to the gut-wall and proceeds to form proglottides.

The presence of the adult tæniæ in the intestinal canal of man may be unaccompanied by any symptoms in the healthy adult, but in debilitated

subjects or in children it may cause gastro-intestinal disturbances, anorexia, vomiting, hyperæsthesia of nervous origin, and severe anæmia.

TÆNIA SAGINATA (Goeze, 1782)

Habitat.—The upper part of the small intestine.

Geographical distribution.—This worm has a world-wide distribution—is found, in fact, wherever ox-flesh is eaten.

Characters.—*T. saginata* is whitish in colour and semi-transparent; a fully adult example measures 4–10 metres, or even longer; it lives in the upper part of the small intestine. The scolex is pear-shaped or cubical, 1–2 mm. in diameter, with four lateral suckers, but without a rostellum or hooks; the suckers are frequently pigmented. (Fig. 246, 4.) In place of the rostellum there is a sucker-like organ at the apex. The neck is fairly long and about half the width of the scolex. The proglottides gradually elongate as they become older; the gravid ones are three or four times longer than they are broad. The genital pore is single, and marginally-placed at the hinder end of each proglottis; in position it alternates irregularly between the right and left margins. There are 20–35 lateral branches on each side of the uterus, and these in turn may actually ramify. (Fig. 247, B.) The eggs are more or less globular, 30–40 μ long and 20–30 μ in diameter. Each is provided with two shells—the egg-shell proper, thin and transparent, and the embryophore, thick and radially striated, containing the onchosphere, with three pairs of embryonal hooklets. (Plate XXXV, 17, facing p. 874.)

Life-history and pathogenesis.—The gravid proglottides pass to the exterior either in the fæces or independently by their own movements. Once outside the body they creep into grass or herbage, and there disintegrate. The eggs are taken into the alimentary canal of the ox, and the onchospheres are set free and pass into the small intestine. After boring their way through the intestinal wall they are carried to muscles in various parts of the body, more especially the pterygoids, the fatty tissues surrounding the heart, the diaphragm, and the tongue. Here they become cysticerci, as in the analogous *T. solium*, 7·5–9 mm. in length by 5·5 mm. in breadth. The cysticerci can live for eight months or thereabouts in the ox, and can only develop further when ingested by man, the definitive host. When this happens the bladder is digested and the liberated scolex passes into the small intestine and affixes itself by means of its suckers to the gut-wall. It is found that the cysts die when heated to a temperature of 48° C.

In the definitive host the parasite may give rise to slight symptoms or may cause a certain degree of anæmia.

Several specimens of human tapeworm—*T. africana*, *T. hominis*, *T. philippina*, *T. bremneri*, *T. confusa*—have been described from time to time as belonging to new species, but they are now held to be aberrant forms or immature examples of *T. saginata*.

Abnormal forms of this tapeworm are very common, and have been described under various names—e.g. *Tænia lophosoma*.

HYMENOLEPIS NANA (Siebold, 1852)

Synonyms.—*Tænia nana*; *Hymenolepis murina*; *H. longior*.

H. nana was originally discovered by Bilharz in Cairo in 1851; Grassi later believed it to be identical with *H. fraterna* of the rat, a view which has recently been confirmed by Woodland as the result of his work in Lisbon.

Habitat.—The small intestine.

The geographical distribution of *H. nana* is limited to warm countries. It is found in Egypt, the Sudan, Siam, Japan, the southern states of the American Union, Brazil, Argentina, and throughout Europe, but more especially in the warmer parts, as in Portugal, Spain, and Sicily, where, according to Calandruccio, 10 per cent. of the children are affected.

Characters.—The strobila of *H. nana* varies in length from 5–45 mm. with the number of proglottides, which may be 100–200. (Fig. 248.) The scolex is subglobular and measures $139\ 480\ \mu$ in diameter; it is provided with a well-developed rostellum armed with a single crown of 20–30 hooklets $14\text{--}18\ \mu$ long; the suckers are globular, and have a diameter of $80\text{--}150\ \mu$. (Fig. 246, 1.) The neck is long. The proglottides are very short anteriorly; farther down they increase in size, but remain broader than long. Only the hindmost segments may equal or even slightly exceed their breadth. The maximum breadth of the proglottides is 0.5–0.9 mm. The genital pores open on the margin near the anterior border of each segment. There are three testes in each segment; the vas deferens widens to form a seminal vesicle. The gravid uterus occupies nearly the entire segment. The eggs number 80–180 in each proglottis; they are oval or globular, and present two distinct membranes; the outer one measures from $40\text{--}46\ \mu$ in diameter, the inner one $20\text{--}34\ \mu$. (Plate XXXV, 20, facing p. 874.) The latter exhibits at each pole a more or less conspicuous mammillate projection, and encloses an onchosphere with three pairs of embryonic hooks. The segments, when set at liberty, are partially digested; the eggs are set free and appear in the fæces, where they can be found by microscopical examination.



Fig. 248.
Hymenolepis nana.
Magnified.

No intermediary host is required, but the larval parasite can enter a villus of the small intestine and become a cysticeroid or a *cercocystis*,¹ the probable mode of evolution being based upon the analogous case of *H. fraterna* in the rat, as worked out by Grassi and Rovelli, and later confirmed by Joyeux and Woodland.

In about 40–70 hours after ingestion the scolex has appeared, and in 80–90 hours the rostellum is provided with hooklets. Then the parasite passes into the lumen of the intestine, where it can be seen attached to the epithelium of the villus with short neck and no trace of segmentation. The rapidity of development varies somewhat, and, as a rule, various stages are found occurring simultaneously in the same host. Strobilization is rapid; the proglottides attain maturity in about 10–12 days, and about 30 days after infection the eggs of the parasite begin to appear in the fæces. The development of the parasite without the aid of an intermediary host and without passing out of the body of the definitive host forms the single exception to the rule that these helminths do not multiply in the body of the definitive host.

Pathogenesis.—*H. nana* is very minute, but, as a rule, it occurs in large

¹ The term *cercocystis* was introduced by Villot to designate those cysticeroids which are provided with caudal appendages.

numbers—usually hundreds, not infrequently thousands. The most frequent symptoms reported by authors are abdominal pain, which may, or may not be associated with diarrhœa; convulsions of various kinds, frequently epileptiform; headache and strabismus. The nervous phenomena are ascribed to the absorption of toxic products elaborated by the parasite. On account of its small size it is easily overlooked. Diagnosis is based on the presence of the characteristic eggs in the fæces. Some care is requisite in looking for the eggs, because, owing to their transparency, they may escape observation.

Treatment.—*H. nana* is readily expelled by male fern or by oil of chenopodium and carbon tetrachloride. A patient harbouring this parasite should not sleep in the same bed with another person.

HYMENOLEPIS DIMINUTA (Rudolphi, 1819)

Habitat.—The small intestine.

Geographical distribution.—*H. diminuta* is a parasite of rats (*Rattus decumanus*, *rattus*, and *alexandrinus*) and mice (*Mus musculus* and *M. sylvaticus*), and has been found in man in Italy, South America, the Congo, and the West Indies, some seventeen cases having been reported.

Characters.—The length is 20–60 cm., the breadth 3·5 mm. The head is very small, cuboidal in shape, with a small infundibulum at the apex in which is a rudimentary rostellum; there are four small suckers, unarmed. The neck is shorter than the head, and the proglottides increase in size, but are considerably broader than long. The eggs as they appear in the fæces are circular or slightly ovoid, measuring 60–86 μ in diameter; the outer shell is yellowish and thickened, with indistinct radiations containing a hexacanth oncosphere.

Life-history.—The cysticercus stage takes place in the body-cavity of certain insects, especially of fleas, *Ceratophyllus fasciatus*, *Xenopsylla cheopis*, *Pulex irritans*, and also certain coleoptera and lepidoptera, *Akis spinosa* and *Scaurus striatus*; the meal-moth, *Pyrallis farinalis*; the earwig, *Anisolabis anulipes*; the meal-worm, *Tenebrio mollitor*; cockroaches, *Periplaneta orientalis* and *Blatta germanica*.

Man becomes accidentally infected, apparently by eating insufficiently-cooked bread in which these insects occur. The rat itself is said to be easily parasitized by eating infected fleas. The cysticercoids, when ingested by their definitive host, become adult in 17 days.

DIPYLIDIUM CANINUM (Linn., 1758)

Habitat.—The small intestine.

Geographical distribution.—*D. caninum* is a common parasite of dogs, cats, and jackals. There are almost 100 records of its occurrence in man, most of them in children in European countries.

Characters.—The strobila measures 15–40 cm. in length and has a maximal breadth of 2–3 mm. The scolex is a small and globular point 0·55 mm. in diameter. The rostellum, which can be retracted into an infundibulum, has three or four circles each consisting of 28–30 small hooklets, 14–18 μ in length. These hooklets are of a characteristic “rose-thorn” shape. There are four elliptical suckers. (Fig. 246, 2.) The proglottides are very narrow, and number 200 or more; the more mature measure 2–3 mm. in breadth and 6–7 mm. in length, so that they are considerably longer than broad.

There are two sets of genital apparatus in each segment, and the genital pores lie symmetrically at the lateral margins. The uterine cavities contain

egg-nests, each with 8–15 eggs, which are round and measure 35–40 μ in diameter. The mature proglottides leave the intestine spontaneously.

As a rule, *D. caninum* infections produce no untoward symptoms. The larval or cysticeroid stage takes place in the dog-louse (*Trichodectes canis*), in the dog-flea (*Ctenocephalus canis*), or in the human flea (*Pulex irritans*).

According to Joyeux, the eggs are eaten by the larval flea, but the development of the hexacanth embryo, which lies in the adipose tissue and muscles of the flea, is delayed until the stage of the flea is reached. Infection in man is caused by swallowing an infected adult flea.

DAVAINEA

The genus *Davainea* is characterized by the presence of numerous hooklets on the suckers, as well as on the rostellum, where they are of a characteristic "coal-hammer" shape. The genital pores are usually unilateral; in the ripe segments the uterus contains eggs. Normally, members of this genus are parasites of birds; more rarely, of mammals.

Three species have been recorded from man: (1) *Davainea asiatica*—one case from Russian Turkestan; (2) *D. formosana*—one from Formosa; and (3) *D. madagascariensis*—eight cases from Mauritius, Siam, the Philippines, and British Guiana.

The life-history is unknown.

LARVAL FORMS OF CYCLOPHYLLIDEA OCCURRING IN MAN

Hydatid, the larval form of *Echinococcus granulosus*, the adult of which occurs in the intestine of the dog.

Cysticercus cellulosæ, the larval form of *T. solium*, in normal circumstances occurring in the pig, but rare in man.

Cysticercus bovis, the larval form of *T. saginata*, which normally occurs in the muscles of the ox, but has been reported in man on a very few occasions.

Cœnurus cerebralis, the larval form of *Tænia (Multiceps) multiceps*, normally occurs in the brain of sheep, and passes the adult stage in the intestine of the dog. One case has been recorded in man.

Cœnurus glomeratus has once been found in a cyst on the chest-wall in man in northern Nigeria, and is normally found in the gerbille. The hooks of the scoleces are distinctive.

ECHINOCOCCUS GRANULOSUS (Batsch, 1786)

Habitat.—The adult worm is a parasite of the dog, wolf, jackal and fox, and occurs in the small intestine of these animals. It is common in Iceland; in Asia—especially in Arabia; in Africa—Algeria, Tunis, Egypt, Abyssinia, and the Cape; in America—Argentina and Uruguay; in Australia—Victoria and Tasmania.

The larval stage of this parasite is the most striking, for after ingestion of the egg by the intermediate mammalian host (sheep, cattle, pigs, camels or man), a hydatid cyst forms in the organs of the body, especially the liver.

Characters.—*E. granulosus* (Fig. 249) is one of the smallest of tapeworms, 2.5–6 mm. in length. The scolex is 0.3 mm. in diameter, irregularly globular in shape, and is provided at its apex with a projecting rostellum which carries two circular rows of hooks of varying size and

number. The neck is short and thick. The proglottides do not number more than four, of which the terminal one is by far the longest, measuring 2-3 mm. in length; it is the only one which is sexually mature, and it may contain as many as 800 eggs. The genital apertures are marginal, one to each proglottis, and have an alternate arrangement. The testes are spherical and numerous; the cirrus pouch is large and pear-shaped. The uterus, tubular, and median in position, has short unbranched lateral diverticula. The eggs are slightly ovoidal in shape, 32-36 μ in length and 21-30 μ in breadth. The onchosphere is provided with three pairs of embryonal hooklets.

The egg is swallowed and in the stomach the shell is digested as the onchosphere escapes. Eight hours after ingestion the parasite appears in the portal vein and reaches the liver. In three weeks it has become vesicular and just visible to the naked eye. In three months it has become 5 cm. in diameter, and within five has doubled its size. The wall of the hydatid cyst is composed of an outer laminated fibrous layer formed by the host, a thick median striated layer secreted by the cyst, and an inner "germinal layer" from which brood-capsules and daughter-cysts arise (Dew).

Two types of development occur, (1) endogenous, (2) exogenous. In the former, proliferation takes place inwards towards the cyst-cavity, while in the latter it takes place in an outward direction.

Brood-capsules are formed from small nuclear masses of the parenchymatous germinal layer; later these become vacuolated to form vesicles. The larval scoleces arise from a local thickening of the wall of the brood-capsule. The wall of the capsule evaginates to form a protective cup for the growing scolex, but near the head end the cuticle thickens and a circle of hooklets develops. There is a contractile part of the body of the scolex capable of invaginating the head, so that the typical resting position of the scolex has the hooklets inside. (Fig. 250.)

Daughter-cysts are produced by some injury or mechanical interference with the mother-cyst. They most commonly arise from the detached germinal layer, but may also develop from brood-capsule cells, or, rarely, by vesicular changes from detached scoleces. Dew and Dévé found that intramuscular or subcutaneous injection of scoleces gives rise to new cysts. This would account for the dissemination of hydatid cysts through the body as sometimes happens after operation.

Exogenous daughter-cysts, which in man are found in the omentum and in bones, are secondary and are caused by herniation of both germinal and laminated layers through the weakened parts of the adventitia resulting from intracystic pressure. By the final exclusion of these herniations new cysts are formed.

Dog, foxes and jackals become infected with the adult parasite by eating the various organs, especially the discarded offal of sheep, in which hydatids occur. The cyst-wall becomes digested and the young tapeworms escape into the small intestine in the customary manner.

Man becomes infected by too close association with the common definitive host, the sheep-dog. The eggs are ingested by using the same dishes as these



Fig. 249.
Echinococcus granulosus. $\times 15$.
(After Leuckart, in Brumpt's "Précis de Parasitologie.")

animals, or by kissing infected dogs; and it is also possible that houseflies may disseminate the eggs from the faeces of these animals. Persons of all ages are liable to infection, but the disease known as hydatid is more common in children under 10 years. The symptoms to which hydatid may give rise are very varied, according to the site of the cyst. They may include symptoms of toxæmia, such as pyrexia, urticaria, and multiform cutaneous eruptions. On the other hand, the fully-developed cyst may appear as a tumour, especially on the liver, and this, on bursting, forms secondary cysts in other organs, or may suppurate and cause general peritonitis. In the brain, hydatids give rise to symptoms of cerebral tumour; while those of the liver, spleen, and peritoneum are liable to simulate malignant growths. Hydatids of the lung give rise to symptoms of compression, with the formation of fluid in the pleural cavity. The kidney may be converted into a mass resembling hydronephrosis.

Diagnosis.—The cystic swelling may possess peculiar physical signs.

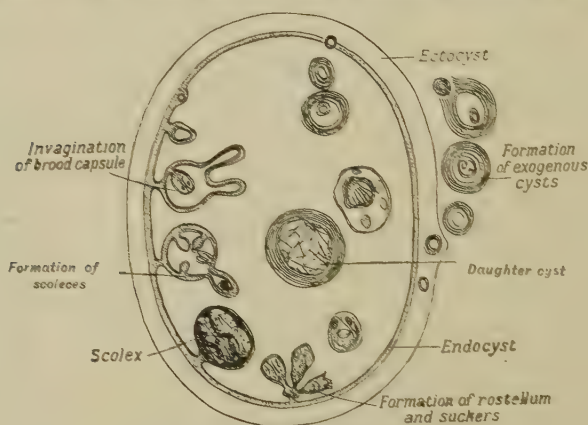


Fig. 250.—Schema of hydatid cyst.
(After Blanchard.)

If it is situated near the surface, a fluctuation, known as the “hydatid thrill,” may be elicited, but if it is deeply seated this is of little value. On puncture of the cyst with an exploratory syringe the scoleces and hooklets may be recognized under the microscope.

Three aids to diagnosis have been described: (1) The precipitin reaction (Welch and Chapman), in which equal parts of preserved hydatid fluid and serum of the suspected case are mingled, the mixture then being incubated for one hour at 37° C. Should the case be infected, a precipitate forms; but one should note that exceptionally this reaction may be given by normal serum. (2) The complement-deviation reaction of Weinberg and Parvu, for which the generally-accepted Wassermann technique is employed, using hydatid fluid (0.4 c.c.) as the antigen. Fairley considers that the best antigen is obtained by macerating the scoleces with absolute alcohol: neither the extract of the cyst-wall nor dried hydatid fluid is satisfactory. Difficulty has so far been experienced in preserving the antigen in an active state. (3) The Casoni, or intradermal test, has been well reported upon by Kellaway

and Dew, who find it of diagnostic value in 90 per cent. of hydatid cases. The fluid is obtained from sheep hydatid, and a few drops instilled by means of a hypodermic needle into the layers of the skin. Within ten minutes of injection, in a positive case, there is produced a large wheal, surrounded by a wide zone of erythema. This fades in an hour, to be followed in six to eight hours by a very large erythema with infiltration and œdema of the subcutaneous tissues. This reaction may be present for several years after surgical removal of the cyst.

Life-history and pathogenesis.—There are two forms of hydatid which occur in man—unilocular and multilocular (or alveolar) hydatid; the former is by far the more common and important. Development takes place as follows: The gravid proglottis is evacuated with the fæces of the host, and by disintegration the eggs are set free. The larval form can develop in other mammals besides man—chiefly in the sheep, ox, pig, camel, goat, and rabbit—and may give rise to severe or, it may be, fatal symptoms. The onchosphere, having passed through the intestinal wall, develops into an hydatid cyst in the liver, lungs, kidney, peritoneum, brain, or genitalia, but occasionally also in other situations, such as the long bones, the heart, and the orbital cavity. The bladder thus produced may attain the size of a human head; surrounding it there develops a fibrous layer formed from the host's tissues. The cyst-wall itself consists of two layers: (a) a cuticular, or laminated layer, composed of a chitinous substance; (b) a germinal layer, made up of an outer layer of small cells and an inner layer of larger ones, together with some muscular fibres, calcareous bodies, and glycogen. The bladder itself is filled with a clear, watery fluid with a specific gravity of 1007–1015, often containing a trace of albumin which is not coagulable by heat or acids, and which is possibly a protein allied to casein. Sodium chloride is present to the extent of 0·5 per cent.; phosphates and sulphates of soda, succinates of sodium and calcium, traces of sugar and inosite are also present. The intracystic toxin is most nearly allied to albumin. The alarming symptoms produced by the accidental rupture of a cyst are probably anaphylactic in nature.

There are two forms of *unilocular* hydatid—primary and secondary; the one is caused by the ingestion of the hexacanth embryo passed in the dog's fæces, as described above; the other by the implantation of a scolex which has been set at liberty by the rupture of a primary hydatid cyst. This scolex undergoes vesicular transformation, and continues to develop on the same lines as a primary hydatid.

Under the designation *multilocular* or *alveolar hydatid* several authorities have described the larval stages of an echinococcus which differs from the development as given above. It was thought that the adult tapeworm might be a different species, and not *E. granulosus*, but this has been proved by Dew to be incorrect. The initial larval stages follow the same development as *E. granulosus*, but after a certain stage of development has been attained, the original cyst throws off germinal buds which become multilocular or alveolar cysts. The liver is generally the seat of this infection, and appears honeycombed with the cysts, which have no cyst-wall.

Surgical treatment in this case is almost impossible, though partial hepatectomy has been practised with apparent success by Brins.

The multilocular form has a peculiar distribution, being found in the Tyrol, Württemberg, Russia, and Siberia.

PHYLUM NEMATHELMINTHES

The Nematelminthes are cylindrical, unsegmented, unisexual worms, having a dorsal and a ventral surface; they are bilaterally symmetrical.

An intestine may be present or absent. There is also a distinct body-cavity (this is not a true coelome, as it is not lined by endothelial cells).

The Nematelminthes are divided into three groups—(1) Nematoda, (2) Acanthocephala, (3) Nematomorpha. The forms which are parasitic in man belong to the group Nematoda.

NEMATODA

The nematodes are cylindrical non-segmented worms, usually tapering at both ends; in colour they are white or yellow, sometimes semi-transparent.

Anatomy.—The *alimentary canal* is complete from mouth to anus, which is subterminal.

The *nervous system*, when present, consists of an oesophageal ring from which a variable number of nerve filaments run in a posterior direction.

The *excretory system* consists of two longitudinal vessels, which unite anteriorly and open on the ventral surface in the median line by an excretory pore.

The *genital organs*.—The sexes are generally separated, the *male* being smaller than the female, and distinguished by a curved or twisted tail, or a cuticular expansion—or bursa—adapted for copulatory purposes. The male organs consist of a long coiled tube, the anterior portion representing the testis; the centre, the vas deferens; while the terminal portion functions as the vesicula seminalis. The ductus ejaculatorius, with glandular walls, terminates near the rectum. The cloaca accommodates one or two chitinous rods, or spicules; these organs are used as specula, and facilitate the entrance of the spermatozoa into the vagina of the female.

The *female* organs consist generally of two coiled tubes. The upper or glandular portion of each tube represents the ovary; the middle, the oviduct; the terminal functions as the uterus. At the junction of the uteri there is a dilatation or a receptaculum seminis. The two uteri join to form a short median vagina, which opens in the mid-ventral line of the anterior half of the body. The upper portion of the uterus is glandular and represents the shell-gland. The uteri are generally distended with eggs already fertilized. In some species a muscular ovjector is present.

Passing along the whole length of the body run four longitudinal lines. Two of these are dorsal and ventral and two lateral. The dorsal and ventral convey the nerve-fibres from the muscles, the lateral the excretory ducts, which join and open ventrally by the excretory pore. The body wall consists of a chitinous skin or cuticle investing the whole body, and a muscular layer composed of longitudinal fibres.

These worms possess a body-cavity filled with amoeboid cells in which the organs lie.

Life-history.—The egg consists of a shell containing a fertilized cell and numerous yolk-granules; it develops further by one of two processes, known as *direct* and *indirect*. In no case are sexually-mature worms produced from fertilized eggs in the host in which the parasites exist.

DIRECT DEVELOPMENT.—This may take place in four different ways, without the aid of an intermediary host :

1. The eggs leave the body in an unsegmented condition and develop in damp ground. When the embryo is fully developed the egg is ingested by its new host. Example, *Trichuris*.

2. The eggs leave the body in a fully-developed condition, and may be taken up immediately by the new host. Example, *Enterobius*.

3. The eggs leave the body in a partly-segmented condition and develop into larvæ outside the body in the fæces and earth and, when mature, enter their new host by boring through the skin. Examples, *Ancylostoma* and *Necator*.

4. The eggs develop on the ground into larvæ which become sexually mature, and, after copulation has taken place, the now fertilized female in turn lays eggs ; these hatch into other larvæ, not sexually differentiated, which themselves re-enter man by boring through the tissues. Example, *Strongyloides stercoralis*.

INDIRECT DEVELOPMENT may take place in three ways :

1. The female nematode in the intestinal canal is viviparous, and the larvæ must enter an intermediary host in order to complete development. In the latter animal they enter the tissues ; here they become mature and encyst. Further development is only possible if the tissues of the intermediary host are eaten by the definitive host. Example, *Trichinella spiralis*.

2. The viviparous female nematode, situated in the connective or lymphatic tissues, produces active embryos which circulate in the blood and are taken up by blood-sucking insects acting as intermediaries. Example, *Filaria bancrofti*.

3. The viviparous female lives in the connective tissues underneath the skin and voids active embryos into water, where they enter into a fresh-water crustacean—which, in this instance, acts as the intermediary host—and are again ingested by man. Example, *Dracunculus medinensis*.

The pathological effects produced by nematodes are described in the text. They are produced in four different ways :

(1) *Mechanical*, by obstruction of the bowel, or blockage of glandular ducts, or even of vessels. Examples, *Ascaris*, *Filaria bancrofti*.

(2) By abstraction of blood, causing anæmia, with secondary effects. Example, *Ancylostoma*.

(3) By excretion and absorption of toxins injurious to the body, as in *Ancylostoma* and *Trichinella*.

(4) By mechanical irritation, causing hyperplasia and overgrowth of specialized tissue. Cyst-formation in the bowel mucosa is produced by *Æsophagostomum* ; hyperplasia of lymphatic glands and tissue by *Filaria bancrofti*.

Considerable interest from the viewpoint of comparative pathology has been aroused by the work of Fibiger on the production of gastric carcinomata in rats by a Spirurid, *Spiroptera neoplastica*. This parasite is capable of giving rise to intestinal growths of a cancerous nature, with the formation of metastases in various organs. The larva of this parasite occurs encysted in cockroaches, *Periplaneta americana*. *Æsophagostomum apiostomum* also causes tumour-formation in the intestine of its host, but not of a malignant character.

CLASSIFICATION OF THE NEMATODES PARASITIC IN MAN

ASCARIDÆ	<i>Ascaris</i>	<i>A. lumbricoides</i>
PHYSALOPTERIDÆ	<i>Physaloptera</i>	<i>P. mordens</i>
STRONGYLIDÆ	<i>Ancylostoma</i>	<i>A. duodenale</i>
	"	<i>A. braziliense</i>
	<i>Necator</i>	<i>N. americanus</i>
	<i>Oesophagostomum</i>	<i>O. apistomum</i>
	<i>Ternidens</i>	<i>T. deminutus</i>
	<i>Trichostrongylus</i>	<i>T. colubriformis</i>
ANGIOSTOMIDÆ	<i>Strongyloides</i>	<i>S. stercoralis</i>
TRICHINELLIDÆ	<i>Trichinella</i>	<i>T. spiralis</i>
TRICHURIDÆ	<i>Trichuris</i>	<i>T. trichiura</i>
	<i>Hepaticola</i>	<i>H. hepatica</i>
OXYURIDÆ	<i>Enterobius</i>	<i>E. vermicularis</i>
FILARIIDÆ	<i>Filaria</i>	<i>F. bancrofti</i>
	"	<i>F. ozzardi</i>
	<i>Acanthocheilonema</i>	<i>A. persians</i>
	<i>Loa</i>	<i>L. loa</i>
	<i>Onchocerca</i>	<i>O. volvulus</i>
DRACUNCULIDÆ	<i>Dracunculus</i>	<i>D. medinensis</i>

For illustrations of eggs of nematodes parasitic in man, see Plate XXXV.

The following nematodes have also been recorded in man, but so rarely as to be of very little importance. They are for the most part parasites of domestic animals which have found their way into man accidentally.

ASCARIDÆ.

Lagochilascaris minor (Leiper, 1909)

This worm, which is normally a parasite of felines in the West Indies and South America, has occasionally been found in subcutaneous abscesses.

Belascaris cati (Schränk, 1788)

Common in the domestic cat all over the world.

Toxascaris canis (Werner, 1782)

Universally parasitic in the dog.

GNATHOSTOMIDÆ.

Gnathostoma.

G. spinigerum (Owen, 1836)

An intestinal parasite of cats in the Far East; occurs occasionally in man in subcutaneous tumours.

EUSTRONGYLIDÆ.

Eustrongylus.

E. visceralis (Gmelin, 1789)

This large worm, measuring 15-40 cm. in length, normally occurs in the pelvis of the kidney of certain mammals—seal, otter, wolf, dog, ox, and horse. It has a wide distribution. In man there are only nine recorded instances.

FILARIIDÆ.

Filaria.

F. conjunctivæ (Addario, 1885)

Mainly a parasite of the horse; there are five recorded instances in man.

Dirofilaria.

D. magalhæsi (R. Blanchard, 1895)

Normal host unknown. A species closely allied to *D. immitis*, which is found in the left ventricle of the dog's heart in tropical countries; one case of this worm from the heart of a Brazilian child has been described by Magalhaes.

Thelazia.

T. callipæda Railliet and Henry, 1910

This parasite, occurring in the eye of the dog, has once been recorded in man in China.

¹ The generic name of *Diectophyme* is recognized by some as having priority; it would follow that this parasite should be known as *D. renale*.

ASCARIS LUMBRICOIDES (Linn., 1758)

ROUND WORM

Habitat.—The small intestine of man and pig. *A. suilla* of the pig is indistinguishable from *A. lumbricoides* occurring in man.

Geographical distribution.—World-wide.

Characters.—The female measures 20–25 cm., the male 15–17 cm. In colour they are pale yellow or brown, with whitish longitudinal lines; in

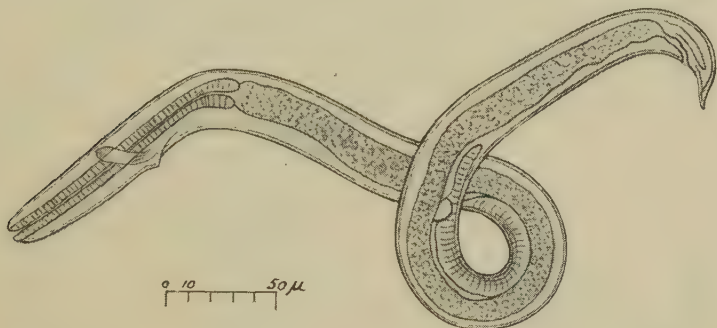


Fig. 251.—Larva of *Ascaris lumbricoides* recovered from the trachea of a rat eight days after ingestion of the eggs of the parasite. (After Brumpt's "Précis de Parasitologie.")

shape they are round, and taper at both ends. The mouth opens at the anterior end, and is guarded by thin lips which have finely denticulated margins. The anus is subterminal. In the male the tail is curved into a semicircle; there are two rows of tactile papillæ and two short chitinous spicules.

The eggs (Plate XXXV, 7, 8, 9, 10, facing p. 874) are elliptical, 50–75 μ in length by 40–50 μ in breadth, and are encased in a rough albuminous coat, giving them a mammillated appearance. They are usually more or less intensely stained by the fæcal pigments.

Life-history.—In the fæces the eggs exhibit no trace of segmentation or of differentiated embryo; but if placed in water, or kept moist and in a warm place, in the course of one or more months—longer or shorter according to temperature—the larva is developed, and can be seen coiled up and moving about inside the egg-shell. Formerly it was held that, if such an egg were accidentally or intentionally swallowed, on arrival in the stomach, the shell would be dissolved away and the contained larva set free; in a month it would grow into a sexually mature animal, and, if both sexes were present, eggs in countless numbers would soon be produced in the fæces.

This view of the life-history of *A. lumbricoides* was based on numerous experiments on man by Continental observers, and until recently seemed to be justified. Stewart, however, has shown that if ripe ascaris eggs are fed

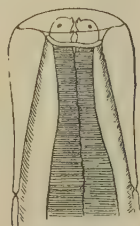


Fig. 252.—Head of *Physaloptera mordens*. (After Leiper.)

to mice and certain other rodents, the larvæ, or a proportion of them, on being hatched out, bore their way into the liver and lungs. In the latter organs they appear in about a week's time, and, if the dose of eggs has been a large one, may cause fatal pneumonia. In experiments made on sucking-pigs, this investigator found that exactly the same process takes place as in rats and mice. For instance, he has found the larvæ abundant in the lungs and trachea on the eighth day; on the ninth they begin to travel down the alimentary canal, and on the following day appear in considerable numbers in the fæces, especially in the colon and cæcum. They measure 1.3–2 mm. on the tenth day, and 1.75–2.37 mm. on the fifteenth. (Fig. 251.) Later observations by Yoshida, Ransom, Foster, Fülleborn, and Brumpt have confirmed this work on guinea-pigs, rabbits, goats, sheep, and monkeys, while the experiments of Mosler and Lutz indicate that the same process

takes place in man. It was proved by Yoshida by experiment on himself that the larvæ from the lung of the rat 8–10 days old became adults in the intestine after a short space of time. An account of the pathogenic effects of the parasite is given at p. 587.

It may give rise to severe symptoms in its wanderings in the intestine.

PHYSALOPTERA MORDENS

(Leiper, 1908)

Habitat.—The œsophagus, stomach, and small intestine. The normal host is a monkey.

Geographical distribution.—Portuguese East Africa, Uganda, and Nyasaland.

Characters.—Both sexes are provided with a mouth guarded by two large lips, each of which is armed with two papillæ and two small rows of teeth. (Fig. 252.)

The male is 30–50 mm. in length; the tail end is provided with two lateral alæ which are formed by expansion of the cuticle, supported by four pairs of pedunculated papillæ. In addition to these there are six pairs of sessile papillæ and one unpaired postanal papilla. There are also two spicules of unequal length.

The female measures 40–55 mm. in length and 2–3 mm. in breadth; the posterior end tapers rapidly, terminating in a sharp point. There are two ovaries and a single uterine tube, and the vulva is situ-



Fig. 253. — *A. duodenale*, male and female, (After Looss.)

ated in the anterior part of the body. The eggs measure $45\ \mu$ in length and $35\ \mu$ in breadth, and are provided with a thick, smooth shell.

ANCYLOSTOMA DUODENALE (Dubini, 1843)

HOOKWORM

Habitat.—The small intestine of man, occasionally in the tiger, young dogs, and cats.

Geographical distribution.—Originally confined to Europe, this parasite has now spread to America, Africa, and Asia, and is found even in northern countries, Germany and England, wherever humidity and temperature are favourable to its development, e.g. the Simplon tunnel and the tin mines of Cornwall. It is very common in Egypt, where in hookworm infections it predominates over the allied species, *Necator americanus*.

Characters.—Both sexes are cylindrical; in colour they are white, grey, or reddish-brown from the presence of blood.

The male measures 8–11 mm. in length and 0.4–0.5 mm. in breadth. (Figs.

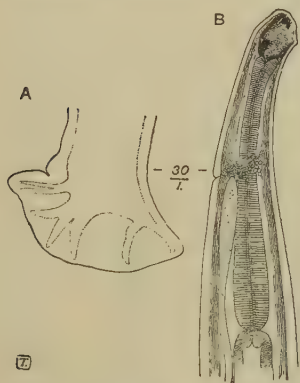


Fig. 254.—Bursa (A) and head (B) of *A. duodenale*.
(After Looss.)

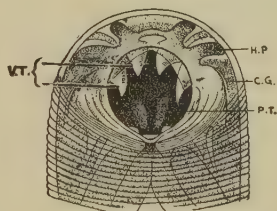


Fig. 255.—Head of *A. duodenale*, showing hook-like ventral teeth.
 $\times 50$. (After Looss.)

c.g., Cephalic gland; h.p., head papillae;
p.t., pharyngeal teeth; v.t., ventral teeth.

149 and 253.) As in all the strongyles, a copulatory bursa is present, the dorsal ray of which is divided towards the distal end into smaller rays, which in turn bifurcate into three unequal portions. (Fig. 254.) Two long and very delicate spicules are present.

The greater part of the body is occupied by the genital organs, a much-coiled testis leading into a vesicula seminalis, and an elongated ejaculatory duct.

The female measures 10–13 mm. in length by 0.6 mm. in breadth. (Fig. 253.)

The number of ancylostomes recovered at autopsy may number 500–1,000. Individuals are apparently long-lived, their life-span being between four and five years. The body is cylindrical and slightly expanded posteriorly. The vagina is situated in the posterior third of the body. The greater part of the body-cavity is occupied by the ovary and much-coiled uterine tubes, containing characteristic eggs. Owing to the situation of the genital openings in both sexes, the worms in copulation assume a Y-shaped figure.

There are two well-marked cephalic glands, which occupy the anterior third of the body in both sexes, and secrete a ferment that prevents the clotting of blood. The buccal capsule is lined with chitin, and contains two pairs of sharp teeth, which lie on the ventral aspect of the buccal cavity; the opening of the mouth is not terminal, but is directed towards the dorsal surface (Fig. 255). The eggs, elliptical in shape, with a transparent shell, measure $60\ \mu$ in length by $40\ \mu$ in breadth. When freshly deposited they contain 2-4 blastomeres each. (Plate XXXV, 14, facing p. 874.)



Fig. 256.—Dorsal ray of *Ancylostoma braziliense*. (After Leiper.)

ANCYLOSTOMA BRAZILIENSE (Gomes, 1910)

Habitat.—This parasite was originally found in dogs and cats in Brazil; shortly afterwards it was described, under the name of *A. ceylanicum*, in the civet cat in Ceylon. For a long time these were considered to belong to two distinct species, but they are now regarded as identical.

Geographical distribution and characters.—*A. braziliense* is found to be fairly common in mixed "hookworm" infections in man in India, the Malay States, and Siam. It is considerably smaller than *A. duodenale*, and the internal pair of ventral teeth are very much smaller than the corresponding teeth of *A. duodenale*. The formation of the rays in the copulatory bursa also differs (Fig. 256). The male is 8.5 mm. in length, and the female 10 mm.; the former has a distinctive bursa. The eggs of *A. braziliense* are indistinguishable from those of *A. duodenale*.

NECATOR AMERICANUS (Stiles, 1902)

Habitat.—The small intestine of man; it also occurs in the gorilla and in the Patas monkey.

This species was originally discovered by Stiles in cases of ancylostomiasis in America, though its range is by no means confined to the New World, as its name would seem to indicate. It has been found southwards from Virginia to Brazil, in Central and West Africa, in India, Ceylon, the Pacific islands, Malaya, and the Philippines. Probably it is as widely diffused as *A. duodenale*; in Ceylon and India it is the commonest species encountered.

Originally a parasite of Africa and Asia, it was introduced into the New World by African slaves.



Fig. 257.—*Necator americanus*. (After Placencia.)

Characters.—*N. americanus* (Fig. 257) is a shorter and more slender worm than *A. duodenale*.

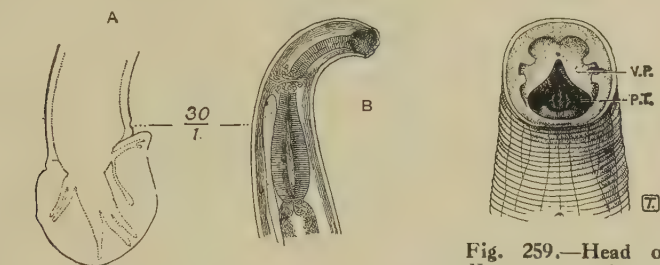


Fig. 258.—Bursa (A) and head (B) of *N. americanus*. (After Looss.)

Fig. 259.—Head of *Necator americanus*, showing pharyngeal teeth (P.T.) and ventral plates (V.P.). $\times 50$.

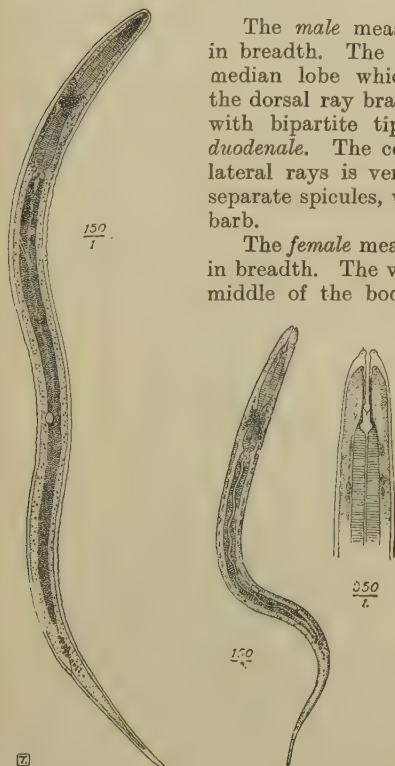


Fig. 260.—Mature larva, young larva, and head of larva of *A. duodenale*. (Partly after Looss.)

The male measures 7–9 mm. in length by 0.3 mm. in breadth. The caudal bursa possesses a short dorso-median lobe which appears as if divided into two; the dorsal ray branches at its base into divergent arms with bipartite tips, instead of tridigitate as in *A. duodenale*. The common base of the dorsal and dorso-lateral rays is very short. (Fig. 258.) There are two separate spicules, which unite to form a single terminal barb.

The female measures 9–11 mm. in length by 0.4 mm. in breadth. The vulva is placed slightly in front of the middle of the body. Copulation of sexes, as in the *A. duodenale*, takes place at the same Y-shaped angle. The pathogenic effects are similar to those of the preceding species (p. 592).

The buccal capsule is smaller than in *A. duodenale* and presents an irregular border; in place of four hook-like teeth, it has a ventral pair of cutting plates; the pair of dorsal teeth is likewise represented by a pair of slightly developed chitinous plates of the same nature. The outlet of the dorsal gland, usually called the dorsal rib or tooth, projects prominently into the oral cavity. Deeply placed in the capsule are one pair of dorsal and one pair of ventral submedian lancets. (Fig. 259.) The eggs are slightly

larger than those of *A. duodenale*, and measure 64–75 μ in length by 36–40 μ in breadth. (Plate XXXV, 15. facing p. 874.)

Summary of the life-history of the hookworms. *Eggs*.—Deposited in the human intestine with two, four, or eight blastomeres; on reaching the outer world they give rise in twenty-four hours to—

Rhabditiform larvæ.—Moult on the third day; on the fifth day the pharyngeal bulb disappears; a second moult takes place and they become filariform larvæ, having a simple muscular œsophagus and a protective sheath; this is the infective stage, and they gain entrance to the body by penetration of the skin or buccal mucous membranes. (Fig. 260.)

On penetrating the skin the sheath is left behind, and the larvæ enter the lymphatics, whence they gain the blood-stream and make their way to the lungs, which they reach on or about the third day. Breaking through the thin-walled alveoli and the lung, they effect entrance into the bronchi, thence via the trachea and œsophagus into the stomach; during this migration the third moult takes place, and a terminal buccal capsule is formed. On arrival in the intestine, which occurs about the seventh day, the fourth moult takes place, and the terminal buccal capsule is changed for what is known as a "provisional buccal capsule," which has a mouth-opening directed dorsally as in the adult worm, but has no teeth. On or about the fifteenth day after entry into the body the provisional buccal capsule is cast, and the worm takes on its adult form, both the adult buccal capsule and bursa of the male being now developed. The worms become sexually mature in three to four weeks, copulation takes place, and fertile eggs are laid.

In the filariform infective stage the embryo, by reason of its sheath, is able to withstand a certain amount of desiccation and extremes of temperature for a considerable period. There is evidence to show that the larvæ can exist alive in warm, damp soil under optimum conditions for upwards of two years. The larvæ are markedly thermotropic, and on the application of a warm surface, such as the sole of the foot or any part of the body, they are immediately aroused to activity and attracted to that spot. (*See also* p. 601.)

ŒSOPHAGOSTOMUM APIOSTOMUM (Willach, 1891)

Habitat.—The cæcum and colon.

Geographical distribution.—West Africa, especially northern Nigeria. This species is known to occur in the gorilla, the orang-outang, and many species of Old World monkeys. In northern Nigeria it is found in about 4 per cent. of prisoners in the jails.

Characters.—In both sexes there is an ovoid expansion of the cuticle at the anterior end, which is limited in front by a salient oral ring and posteriorly by a constriction which is especially marked on the ventral surface 200 μ distant from the oral vestibule; this in turn is provided with a crown of 12 sharp, chitinous plates directed forwards and inwards. (Fig. 261.)

The male is 17–22 mm. in length by 0.75 mm. in breadth; the copulatory bursa has a dorsal ray which bifurcates into two branches, forming a horse-shoe-shaped structure; each limb gives off a short lateral horn near its base. (Fig. 261, c.)

The female is 25–30 mm. in length by 1 mm. in breadth. Posteriorly she terminates in a sharp point; the vulva is situated in the anterior half of the body.

The eggs are passed in an advanced stage of development, and measure 60 μ in length by 40 μ in breadth.

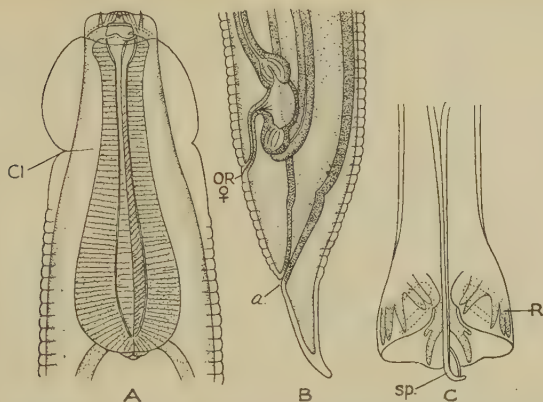


Fig. 261.—*Esophagostomum apiostomum*. (Partly after Railliet and Henry.)

A, Head, showing cuticular expansion and oval vestibule. B, Tail of female. C, Tail of male, showing copulatory bursa.
a., Anus; Cl., ventral cleft; OR., vaginal orifice; R., characteristic rays of bursa; Sp., spicule.

Pathogenesis.—These worms are found both free and encysted under the mucous membrane of the large gut, usually in the cæcum.

If the infection is severe the worms may give rise to dysenteric symptoms.

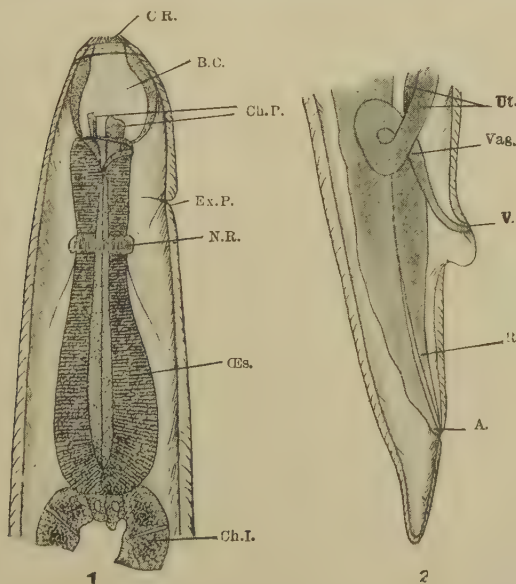


Fig. 262.—*Ternidens deminutus*, female. (After Leiper.)

1, Anterior extremity. 2, Posterior extremity. C.R., corona radiata. B.C., buccal cavity. Ch.P., chitinous plates; N.R., nerve-ring CEs., cesophagus; Ch.I., chyle intest. Ut., uterus; Vag., vagina V., vaginal opening; R., rectum; A., anus.

TERNIDENS DEMINUTUS (Railliet and Henry, 1905)

Habitat.—The large intestine of monkeys, *Macacus sinicus* and *M. cynomolgus*, and has been found in man.

Geographical distribution.—This is a not uncommon parasite of man in the Transvaal and in Nyasaland, but, unless it occurs in large numbers, is of no pathological importance.

Characters.—The worm resembles a female ancylostome in size, but the anterior extremity is not bent as in the hook-worms, and the mouth-capsule opens terminally and has a corona of setæ. At the base of the large cup-like buccal capsule are three serrated teeth which guard the entrance to the œsophagus. These teeth are characteristic of the genus *Ternidens*. (Fig. 262.)

The male is 9.5 mm. long by 0.56 mm. broad. The dorsal ray of the copulatory bursa divides into two towards its distal extremity, and each of the branches formed again bifurcates. (Fig. 263.)

The female is 14–16 mm. in length and 0.73 mm. in breadth. The genital orifice is posterior and subterminal. The vagina is short and opens into two uterine tubes. The eggs are delicate, transparent, and oval, measure 60 μ in length by 40 μ in breadth, and are passed in an advanced stage of segmentation.



Fig. 263.—Bursa of *Ternidens deminutus*, ♂. (After Brumpt.)

TRICHOSTRONGYLUS COLUBRIFORMIS (Giles 1892)

Habitat.—This nematode occurs not infrequently in the upper part of the small intestine.

Geographical distribution.—India, Japan, Egypt and Central Africa.



Fig. 264.—*T. colubiformis*, female. $\times 25$.

Characters.—Originally described by Looss in man, it is normally a parasite of the sheep or goat; it is found frequently in Japan and Korea. By using the flotation technique in detection of the eggs in the fæces, Lane finds it is commoner in the fæces of ancylostome patients than has been supposed, and Chandler records it in 10 per cent. of cases in Assam. The females (Fig. 264) greatly outnumber the males and measure 4–6.5 mm. In colour pale pink, the anterior extremity is attenuated. The vulva is situated in the posterior quarter of the body. The male (Fig. 265) is 4–5 mm. in length by 0.07 mm. in breadth and is provided with a bilobed copulatory bursa and two spicules. This parasite does not occur in large numbers in man; the mouth is unarmed, and on this account, as well as of its small size, it does not give rise to any particular symptoms. The eggs (63 μ by 41 μ) are relatively large; they are oval, thin-shelled and contain a morula at oviposition. On account of their general resemblance they are apt to be mistaken in fæces for those of the ancylostome, but they are more translucent and smaller in size.

The Eastern form has been separated as *Trichostrongylus orientalis*.

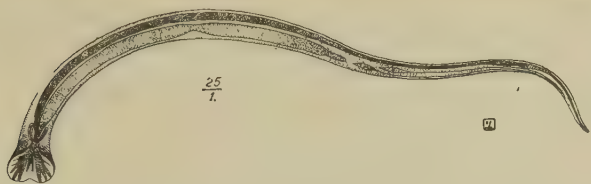


Fig. 265.—*Trichostrongylus colubriformis*, male. $\times 25$.

STRONGYLOIDES STERCORALIS (Bavay, 1876)

Habitat.—The parasitic form of this nematode lives in the submucous tissue of the small intestine.

Geographical distribution.—Almost world-wide, but especially common in Brazil and Cochin China.

Characters.—The parasitic form is a parthenogenetic female, 2.5 mm. long by 0.034 mm. broad, which has no corresponding male. (Fig. 266, 1.) The body tapers anteriorly and ends in a conical tail. The mouth has three small lips which give access to an oesophagus occupying a quarter of the length of the body. The vulva is in the posterior third of the body, and the prominent uterus contains 50 eggs measuring 50–58 μ long by 30–34 broad. The eggs are laid in the lumen of the bowel in a very advanced stage of development. Hatching almost immediately, they give rise to rhabditiform embryos which measure 0.2–0.3 mm. in length by 0.013 mm. in breadth; these possess the characteristic double-bulbed oesophagus, and may easily be confused with the rhabditiform stage of *Ancylostoma* or *Necator* (Figs. 266, 2, and 258). In this stage the embryos are passed in the fæces. In three to five days the larvæ develop into free-living male and female forms.

Both sexes possess a remarkable rhabditiform or double-bulbed muscular oesophagus. The male free-living form measures 0.7 mm. in length by 0.035 mm. (Fig. 266, 3.) The tail is curved ventrally, and two spicules and an accessory piece are present. The female free-living form measures 1 mm. in length by 0.05 mm. in breadth. The vulva is situated a little behind the middle of the body; the uterus usually contains several thin-shelled eggs, 70 μ in length by 40 μ in breadth. (Fig. 266, 4.) Copulation between the sexes takes place in the fæces, and, as a result, rhabditiform embryos are produced which are indistinguishable from the rhabditiform embryos derived from the parthenogenetic and parasitic female.

Life-history.—These rhabditiform embryos, after three or four days, develop into long filariform larvæ which are the infective stage of the parasite and which may re-enter the definitive host via the skin or buccal mucosa in the same manner as the embryos of *Ancylostoma* and *Necator* gain entrance into their host. The filariform larvæ find their way into the small intestine and develop there into the parasitic, parthenogenetic female form. In certain circumstances, e.g. unsuitable climatic conditions, the sexual phase which takes place in the fæces may be omitted, and the rhabditiform embryos produced by the parthenogenetic female may directly develop into the filariform embryos which are capable of infecting the definitive host. (Fig. 266, 5.)

The filariform stage of *Strongyloides* is liable to be confused with that of the same stage of *Ancylostoma* or *Necator*, but microscopical examination

will reveal the fact that, whereas in the former the œsophagus is about half the length of the body, in both the latter it occupies but a quarter (see Fig 266).

Subjoined is a summary of the life-history of *S. stercoralis* :

Evolution of S. stercoralis.—Parthenogenetic intestinal form gives rise to—

Eggs,

which, hatching in the intestinal canal of man, give rise to—

First rhabditiform larvæ in the fæces. At high atmospheric tem-

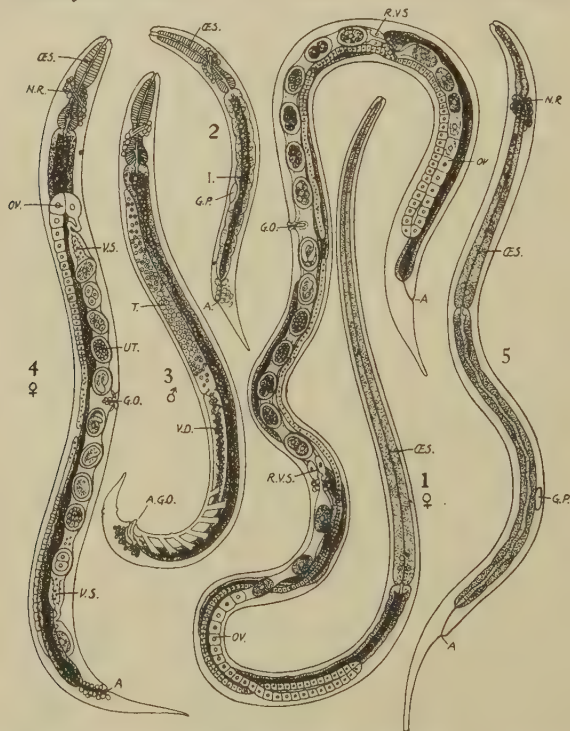


Fig. 266.—Life-history of *Strongyloides stercoralis*. (After Looss.)

1 Parthenogenetic female; 2 rhabditiform embryo; 3, fully-grown male; 4, fully-grown female; 5, fully-developed filariform larva.

A., anus; A.G.O., combined anus and genital pore; G.O., genital opening; G.P., primitive genital organs; I., intestine; N.R., nerve-ring; œs., œsophagus; OV., ovary; R.V.S., rudimentary vesicula seminalis; T., testis; UT., uterus; V.D., vas deferens; V.S., vesicula seminalis.

perature these larvæ give rise either to *infective* or to *sexual* forms, which copulate, and the females lay

Eggs,

from which emerge—

Second rhabditiform larvæ. These moult and give rise to filariform larvæ, which enter man either by penetrating the skin or through the mouth, and develop within two weeks into—

The *parthenogenetic parasitic female* in the small intestine.

Pathogenesis and treatment.—This parasite must undoubtedly produce considerable irritation of the bowel, which may give rise to diarrhoea.

It is usually present in large numbers, and has been found coiled up in the intestinal follicles. The larvæ, after entering the skin, pursue a migration through the lungs and œsophagus similar to that of *Ancylostoma* and of *Necator*. No efficient treatment has yet been devised.

Fülleborn has shown that in persons infected with *S. stercoralis* a super-sensitization to the antigens of this parasite exists. Itchy urticarial wheals are produced at the site of entry of further infecting larvæ in these persons, or even by rubbing into the skin dried extracts of strongyloides larvæ.

The prophylaxis is, naturally, as for *Ancylostoma*.

ENTEROBIUS VERMICULARIS (Linn., 1758)

THREADWORM

Synonym.—*Oxyuris vermicularis*.

Habitat.—Upper part of the large intestine, especially the cæcum; occasionally invades the female genital organs and bladder; more rarely it occurs in the ear and nose.

Geographical distribution.—World-wide.

Characters.—These worms are small and white in colour. The mouth is surrounded by a cuticular expansion; the œsophagus in both sexes is provided with an extra bulb (Fig. 267).

The *male* (Fig. 267, B) is much smaller than the female, and is relatively uncommon. It measures 2.5 mm. in length; the posterior third is curved spirally. The caudal extremity is blunt, and possesses 6 sensory papillæ. A single spicule is present, and measures 70 μ in length. (Fig. 267, c.)

The *female* measures 9–12 mm. in length and has a long pointed tail. The anus is situated 2 mm. from the posterior extremity; the vulva, transverse and slit-like, is situated in the anterior fourth of the body. (Fig. 267, A.)

The eggs measure 50–54 μ in length and 20–27 μ in breadth. They have a characteristic shape, being flattened on one side. There are two shells: the outer is thick and transparent; the inner thin, and containing a more or less fully-formed embryo. (Plate XXXV, 19.)

Life-history and pathogenesis.—The fertilized females migrate out of the anus and deposit their eggs in the natal folds. After a few hours have elapsed the embryos develop rapidly and attain a length of 140–150 μ . At this stage the eggs are ingested, being usually carried by the fingers to the mouth, and on coming in contact with the digestive juices they hatch. The larvæ thus liberated pass after two moults into the large intestine, where they become mature. The duration of the cycle is two weeks.

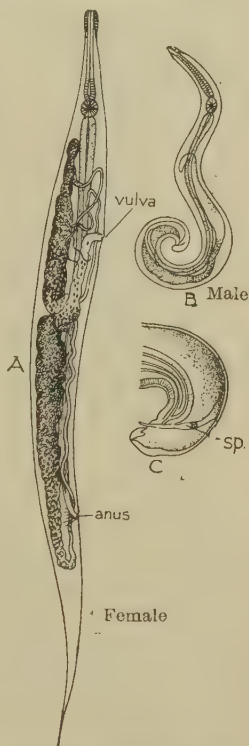


Fig. 267.—*Enterobius vermicularis*. Magnified.
(After Leuckart, in Brumpt's "Précis de Parasitologie.")

Mature worms are capable of penetrating the mucosa and of encysting in the submucosa of the small intestine or appendix, where they may cause inflammation.

Treatment.—Oxyuriasis is often, especially in adults, an extremely difficult condition to treat. General measures, such as the wearing of sleeping-drawers of strong cotton and cotton gloves at night, the paring of the fingernails, washing the hands carefully after defæcation, must be adopted. To prevent itching of the anus and to assist in prevention of the re-infection the anus should be smeared at night-time with some mercurial ointment, as the ung. hydrarg. ammon. B.P.

The worms are expelled per rectum by means of quassia; the rectum should first be evacuated by a hot-water enema or salt-and-water enema (one tablespoonful of salt to half-a-pint). After the bowel has been emptied, the infusion of quassia, diluted 1:100, is injected slowly per rectum, and the foot of the bed raised so as to allow it to percolate through the gut. Keratin-coated quassia pills (2 gr.) may be given by the mouth, morning and evening, and appear to exert a toxic action on the worms if given in conjunction with 1-oz. doses of decoction of aloes every morning.

“Butolan,” p-benzyl phenolcarbamin acidester (Bayer & Co.), given by the mouth in doses of 0.5 grm. three times daily for an adult, and persisted in for a week, or half that quantity for children under 10 years of age, has been highly spoken of. Oxyfax made up in chocolate tablets each containing 0.15 grm. has been employed with good results. *Tubera jalapæ* and 0.1 grm, dihydroxyphthalophenol in the dose of one tablet daily for four weeks is said to be effective in expelling the worms. Garlic used as an infusion has a reputation. The infusion should be prepared by boiling the small roots in a litre of water for one hour, and injected per rectum.

The adoption of a strict diabetic diet is sometimes advisable.

TRICHURIS TRICHIURA (Linn., 1771)

WHIPWORM (Fig. 268)

Synonym.—*Trichocephalus dispar*.

Habitat.—The large intestine, especially the cæcum. It is said to be identical with a species found in the pig.

Geographical distribution.—Cosmopolitan.

Characters.—These worms are greyish-white or slightly pink in colour.

The *male* is 30–45 mm. in length; the anterior attenuated portion, which contains the simple cellular oesophagus, is half as long again as the thicker posterior body portion. The caudal extremity is curved ventrally, and there is a single spicule enclosed in a sheath which itself is closely studded with spines. (Fig. 268, 3.)

The *female* is 30–50 mm. in length, while the anterior attenuated end is twice as long as the posterior. The *eggs*, of a characteristic barrel shape, are brown in colour and measure 50 μ in length by 22 μ in breadth. (Plate xxxv, 18, facing p. 874.)

Life-history and pathogenesis.—On leaving the body the eggs are unsegmented and the contained embryo develops but slowly, attaining its full length in 6–12 months. Owing to its thick shell, it can withstand a low temperature. The embryos can live, without developing any further, apparently, for as long a period as five years. Development is direct; once ingested, the larvæ attain maturity within a month, and probably, like *ascaris*, reach the gut via the liver and lungs.

The worm lives chiefly in the cæcum. In many countries it is present in more than half the population. It maintains its position by transfixing, pin-fashion, with its long slender neck, a superficial fold of the mucous membrane. Wichmann claims to have shown, by serial sections of the cæcum at sites where the parasites were fixed, that it is merely embedded in the mucus between the intestinal villi. According to Powell, the females very much preponderate, the proportion to males being as 466 to 1. Except that the practitioner should be familiar with the appearance of its eggs in the stool (Plate XXXV, 18), so that he may distinguish them from those of *Ascaris*, of *Ancylostoma*, and of other parasites, the presence of *T. trichiura*

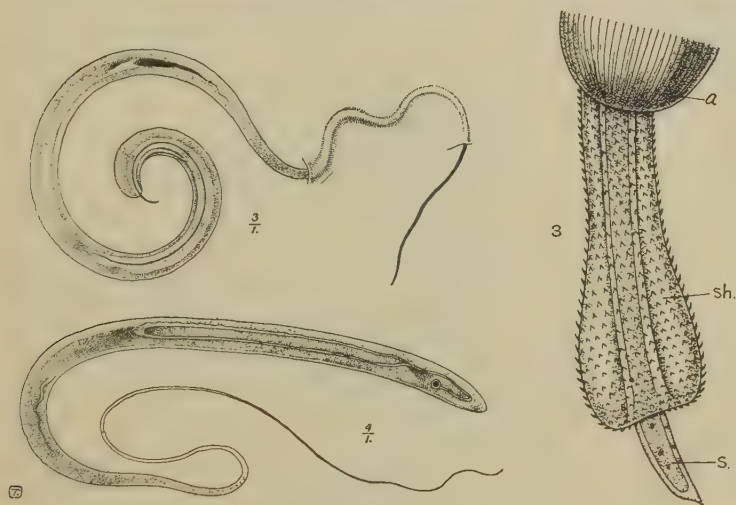


Fig. 268.—*Trichuris trichiura*:

- 1, Male, partly embedded in the mucous membrane of the intestine; 2, female
- 3, copulatory apparatus, greatly magnified.
- a, Posterior extremity of body: s., spicule; sh., sheath.

is of no practical moment. So far as known, it gives rise to no serious pathological lesion; a fortunate circumstance, seeing that hitherto it has been found impossible, with any degree of certainty, to dislodge it by anthelmintics.

HEPATICOLA HEPATICA (Bancroft, 1893) Hall, 1916

This parasite belongs to the family Trichuridae, and is closely allied to *T. trichiura*; it is normally a parasite of the rat, infecting the liver, where it deposits masses of characteristic trichiuris-like eggs in the substance of that organ.

A case of this infection has been reported by Dive and MacArthur as occurring in a British soldier in India. Death took place from septic pneumonia secondary to an abscess of the liver caused by accumulations of adult worms, characteristic masses of eggs of *H. hepatica* being found in the liver-substance.

TRICHINELLA SPIRALIS (Owen, 1835)

Habitat.—The muscles, especially the laryngeal, the diaphragm, and the intercostals.

Geographical distribution.—This is world-wide. In Europe, *Trichinella* was formerly common in Germany until the most stringent prophylactic measures were taken. In America it is still very common; in Boston, for instance, it is estimated that in the municipal slaughter-houses 5 per cent. of the pigs are infected. In Asia it has been found in China and India; and epidemics have been reported in Syria from eating the flesh of naturally-infected wild boars. In Africa it is found in Algeria and in the East African Protectorates. It has been reported occasionally from Australia. Pigs become infected most frequently by eating garbage from abattoirs.

Characters.—*Trichinella* is a white worm just visible to the naked eye. The male (Fig. 269) is 1.6 mm. in length by 0.04 mm. in breadth; the cloaca, situated posteriorly between two caudal appendages, is provided with two pairs of papillæ. The female (Fig. 269) is viviparous, 3–4 mm. in length by 0.06 mm. in breadth; the vulva is situated in the anterior fifth, the posterior half of the body being occupied by the ovary, the anterior by a much-coiled uterine tube. The anus is terminal.

Life-history.—The worms inhabit the small intestine. The young which the female emits migrate into the muscles, where they encyst. In a natural state the pig, wild boar, and rat act as hosts in addition to man, but the majority of animals, even lizards, are capable of being infected under artificial conditions. Birds, however, are refractory.

Infection of a fresh host is brought about by ingestion of raw flesh of a trichinosed animal—that is, one in whose muscles the larval trichinellæ are encysted. Man becomes diseased in this manner by eating uncooked pork. The development of adults from

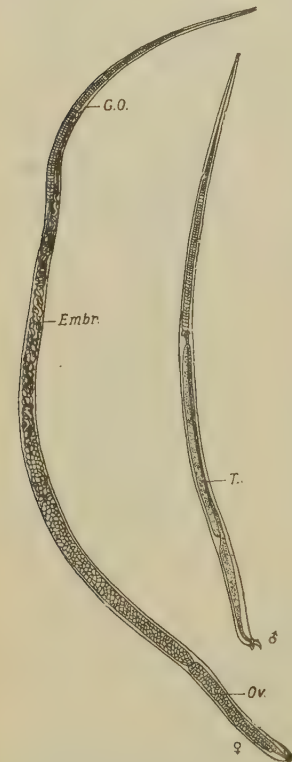


Fig. 269.—*Trichinella spiralis*, female and male.
× 45. (After Brumpt.)

G.O., Genital opening; Embr., embryos; Ov., ovary; T., testis.

larvæ would appear to take place with astounding rapidity, and in as short a period as 48 hours after ingestion it is said that mature male and female worms can be found in the intestine. After a further 24 hours, embryos have already appeared in the uterus of the fertilized female.

The eggs, measuring 20 μ , are found in the upper portion of the uterus, but soon the contained embryo breaks loose and lives free in the uterine cavity. The living embryos are voided into the lumen of the intestine, and measure 100 μ in length by 6 μ in breadth. Travelling independently via

the lymphatics, and to some extent also via the venous channel, and guided by a mysterious instinct, these embryos pierce the coats of the containing vessels and encyst in striated muscular tissues, especially that of the diaphragm, the intercostal and laryngeal muscles, and those of the neck and eye, especially at their tendinous insertions. The cysts themselves are oval in shape, the cyst-wall being formed by the reaction of the tissues. (Fig. 270.) In these situations the embryos may remain alive for a period of five years, if not longer, but, generally speaking, they become calcified after a sojourn of a few months or years.

Pathogenesis.—Both the mature parasites and the larvæ produce the most profound pathological effects. The numerous adults cause an intense catarrhal inflammation of the intestinal canal, and by the hæmorrhages

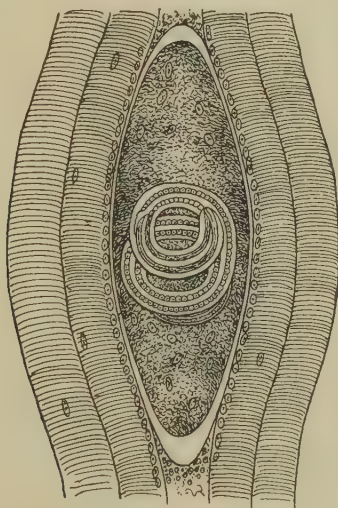


Fig. 270.—Encysted Larva of *Trichinella spiralis*, fifteen days after entering muscle. $\times 300$. (After Claus, in Brumpt's "Précis de Parasitologie.")

they induce may lead to death. The objective symptoms of this stage may resemble those of cholera, or possibly those of dysentery, with passage of blood-stained stools, associated with hyperpyrexia (temperature 104° – 106° F.). During the migration of the larvæ through the tissues typhoidal symptoms predominate, with remittent temperature and slow muttering delirium, merging into rheumatic muscular pains, difficulty in mastication, deglutition, and respiration. Three weeks after infection, while the embryos are encysting in the muscles, a profound cachexia, probably due to absorption of the toxins from the larval trichinellæ, supervenes. Œdema of the face, abdomen, and legs is often noted. Together with this there are mental apathy, intense pruritus, and sometimes skin eruptions. Death may take place in the sixth or seventh week, from exhaustion or from pulmonary complications. In the cases which survive, the fever gradually resolves, but muscular pains of varied intensity persist.

Diagnosis.—The early intestinal symptoms must not be confused with

ptomaine poisoning, cholera, or dysentery. The debility, delirium, and remittent pyrexia may suggest typhoid; the oedema may be mistaken for that of nephritis, though, of course, the urine is free from albumin. From these conditions trichinosis may be differentiated by the high eosinophilia of the blood, by the absence of the Widal reaction, and by the discovery of the adult worms and, in the later stages of the disease, of the embryos in the faeces. In the more chronic rheumatoid stages the characteristic encysted larvæ can be recognized under the microscope in a small portion of muscular tissue removed for this purpose.

Prophylaxis.—In order to render trichinosed meat safe for consumption it is necessary to boil it for a period of half-an-hour for every pound of flesh. The process of curing raw ham (essentially the most common source of trichinosis) by saltpetre would appear to kill only those larvæ which are situated in the most superficial tissues, while those in the deeper layers escape. Curing hams by smoke, as practised in Westphalia, appears to exert no lethal action whatsoever upon the trichinellæ.

FILARIA BANCROFTI (Cobbold, 1877¹)

Habitat.—The lymphatic vessels and glands of man.

Geographical distribution.—The parasite has a wide tropical and sub-tropical distribution, and has been found as far north as Spain in Europe, and as far south as Brisbane, Australia.

Characters.—*F. bancrofti* is a thread-like, white worm found in lymphatic glands and vessels. The sexes are generally coiled together, and can only with difficulty be separated.

The male is 40 mm. in length by 0.1 mm. in breadth, and generally lies coiled up with a markedly corkscrew-like tail. Two spicules of unequal size and an accessory piece are present. The larger spicule, 500 μ in length, has a short, thick proximal portion, and a long whip-like distal portion ending with a hook. The shorter spicule is grooved on its ventral aspect, and measures 200 μ in length. The accessory piece is crescentic. There are 15 pairs of minute caudal papillæ. (Fig. 271, a.)

The female measures 65–100 mm. in length by 0.20–0.28 mm. in breadth; the genital opening is situated 0.6–1.3 mm. from the anterior end, which is tapering and ends in a rounded swelling; the caudal extremity is narrow, but abruptly rounded. (Fig. 271, c.) The eggs in the upper part of the uterus contain well-formed embryos enclosed in a membrane which subsequently becomes the sheath of the living microfilaria. (Fig. 271.) These embryos emitted by the viviparous female find their way by the lymphatics into the blood-stream and are taken up by various species of mosquito of the genera *Culex*, *Aedes* (*Stegomyia*), and *Anopheles*, in whose thoracic muscles they develop.

The embryos of all the Filaridæ are generally known as microfilariae.

Description of embryo (microfilaria).—When examined with a low power, the embryo appears to be structureless; with a high power a certain amount of structure can, on close scrutiny, be made out. In the first place, it can be seen that the entire embryo is enclosed in an exceedingly delicate

¹ As this familiar species does not conform with the genotype of the genus *Filaria*, namely *Filaria martis*, it may be necessary to create a new genus for its reception. The absence of cuticular alæ at the caudal extremity of the male, the position of the female genital opening, and the fact that the species is viviparous, are sufficient to separate it from the genus *Filaria*.

limp, structureless sac, in which it moves backwards and forwards. This sac, or "sheath," as it is generally called, although closely applied to the body, is considerably longer than the enclosed embryo; so that that part of the sac which for the time being is not occupied is collapsed and trails after the head, or tail, or both, as the case may be. It can be seen also that

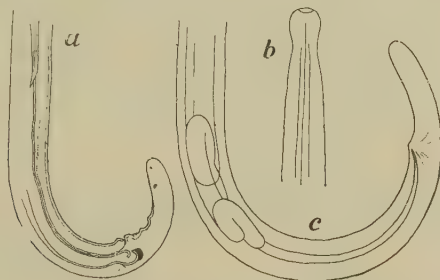


Fig. 271.—Parental forms of *F. bancrofti*. Magnified.

a, Tail of male; b, head and neck; c, tail of female.

about the posterior part of the middle third of the parasite there is what appears to be an irregular aggregation of granular material which, by suitable staining, can be shown to be a viscus of some sort (*Innenkörper*). (Fig. 273.) Further, if a high power be used, a closely set, very delicate transverse striation can be detected in the musculo-cutaneous layer throughout the entire length of the embryo. Besides this, if carefully looked for at a point about one-fifth of the entire length of the organism backwards from the head end, a shining,



Fig. 272.—Evolution of sheathed microfilaria from ovum in uterus of parent worm. The later stages may occasionally take place after emission from vagina. (Partly after Penel.)

triangular V-shaped patch is always visible. What may be this V-spot is brought out by very light staining with dilute hæmatoxylin. The dye brings out yet another spot similar to the preceding, though very much smaller; this second spot is situated a short distance from the end of the tail. The former has been designated the V-spot, the latter the tail-spot. These spots are probably connected with development, the V-spot being the rudiment of the future water-vascular system, the tail-spot that of the anus or

cloaca and terminal part of the alimentary canal. Staining with hæmatoxylin also shows that the body of the embryo is principally composed of a column of closely packed, exceedingly minute cells enclosed in a transversely striated musculo-cutaneous cylinder; at all events, many nuclei are thereby rendered visible. Low has pointed out that the break seen in all stained specimens in the central column of nuclei occurs at a point slightly anterior to the V-spot; this is the position of the nerve-ring. This break can only be recognized in stained preparations. The sheath of the microfilaria represents the chorionic envelope of the ovum, and is stretched out as the embryo uncoils itself on leaving the parental uterus. (Fig. 272.)

When the movements of the living microfilariae have almost ceased, by careful focusing it can be seen that the head end is constantly being covered

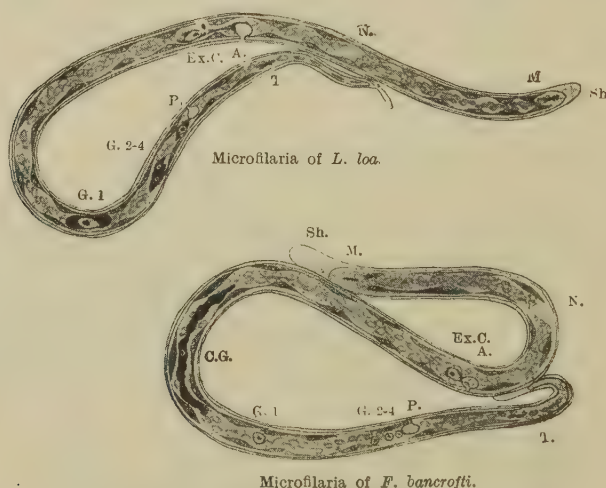


Fig. 273.—Minute anatomy of a microfilaria, and differential points of structure between embryo of *L. loa* and of *F. bancrofti*.
(After Fülleborn.)

N., Nerve-ring (ant. break in cell column); A., ant. V-spot (exc. pore); Ex.C., excretory cell; c.g., granular mass (or *Innenkörper*); G. 1-4, genital cells; P., posterior V- or tail-spot; M., granules in mouth-cavity; T., granules in tail; Sh., sheath.

and uncovered by a very delicate prepuce; moreover, one can sometimes see a short fang of extreme tenuity, based apparently on a highly retractile granule, suddenly shot out from the uncovered extreme cephalic end, and as suddenly retracted (Fig. 118, p. 538), and in a fresh blood preparation it can be seen disturbing the red cells at some distance away.

Filarial periodicity.—The microfilariae of the species exhibit what is known as nocturnal periodicity—that is to say, they are present in the peripheral blood in larger numbers during the night than during the day. In the West Indies, India, and China the maximum concentration of embryos in the peripheral blood occurs between 10 p.m. and 2 a.m. It is thought that this nocturnal periodicity is an adaptation to the habits of the intermediary host, which in this case is a night-biting mosquito, *Culex fatigans*.

On the other hand, the microfilariae which are found in the blood of the inhabitants of some of the Pacific islands (e.g. Fiji, Samoa, Tokelau, Wallis, Ellice Islands, Philippines, and Tahiti), although at present considered on morphological grounds to be identical with the microfilariae of *F. bancrofti*, do not exhibit this nocturnal periodicity, but appear in the blood-stream in equal numbers during the day- and night-time (non-periodic). As this microfilaria develops in a purely diurnal mosquito intermediary, namely *Aedes variegatus* (*Stegomyia pseudoscutellaris*), it is considered by some to be specifically different from *F. bancrofti*, which occurs in other parts of the tropics. As far as is at present known, the adults of the non-periodic microfilaria are morphologically identical with *F. bancrofti*. It is possible that the former variety of *F. bancrofti* represents a species distinct in the biological sense.

Life-history.—Further development of the embryo into the stage known as the larval filaria takes place in the thorax of various species of mosquito. Within an hour-and-a-half of entering the mosquito's stomach, the micro-

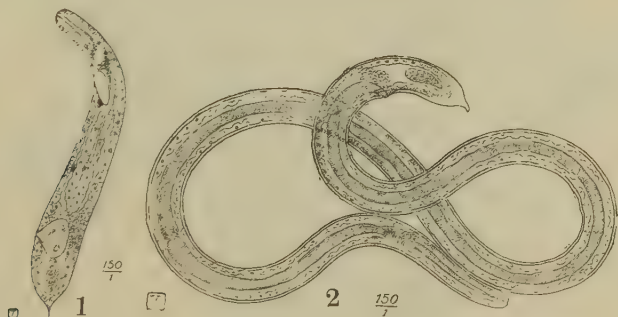


Fig. 274.—Stages of larval form of *F. bancrofti*, from thoracic muscles of *Culex fatigans*. (After Looss.)

filariae cast their sheaths, and within 24 hours the majority have entered the thorax, where they come to lie between the wing muscles. Within the next two days the larval filaria increases greatly in girth, and the posterior V-spot now enlarges; and shortly afterwards the anterior V-spot, or excretory pore, similarly becomes much more prominent. By rapid nuclear proliferation the larval filaria assumes a squat "sausage" form (Fig. 274, 1); the tail now shrinks and is absorbed. The mouth and œsophagus become apparent from the fifth day onwards, and at the same time the posterior V-spot now becomes transformed into the anus. (Fig. 274, 2.)

The œsophagus at this stage has a bulbar enlargement at the first and second fourths of the alimentary canal at a time when the larva is 0.5 mm. in length. The larva, now elongated and worm-like, commences to move about the thorax with sluggish undulating movements. The alimentary canal being complete, the caudal papillae appear; they are three in number, and subterminal, and their function is probably to assist the filaria to progress, and thereby facilitate its subsequent penetration of the skin. Towards the tenth day, in the most favourable circumstances, the snake-like larval filaria, now measuring 1.4 mm., travels forward through the thorax into the head, where it lies coiled up, ready to enter the proboscis sheath of the

mosquito. It may also be occasionally found in the abdominal cavity or legs of the insect. (Figs. 275, 276, 277.)

Under conditions of high temperature and moisture the complete cycle takes 10-14 days, but development may be retarded by cold to six weeks or more. Sometimes the larva, during development, dies in the thoracic muscles and becomes encased in chitin, producing the peculiar structure seen in Fig. 123, p. 544. When the infected mosquito begins to bite another individual man, the larvæ, attracted by the warmth of the skin, break their way through the terminal portion of the proboscis sheath of the insect, known as Dutton's



Fig. 275.—Section of thoracic muscles of *Aedes variegatus*: second day after feeding on filariated patient. (Orig.)

membrane, and, wriggling out on to the skin, rapidly penetrate it near the seat of puncture caused by the stylets of the mosquito. (Figs. 278, 279.) Formerly it was supposed that the mosquito actually injected the larval filaria into the tissues of the victim, but this has been disproved.

Complete development of the larval *Filaria bancrofti* has been observed in the following species of mosquito:

- (1) *Culex fatigans*. West Indies, India, Philippines, and the Pacific.
- (2) *Culex pipiens*. China.
- (3) *Aedes variegatus*, syn. *Stegomyia pseudoscutellaris*. Pacific islands.
- (4) *Aedes (Finlaya) togoi*. Japan.
- (5) *Aedes chemulpaensis*. Japan.
- (6) *Tæniorhynchus (Munsonioides) africanus*. Central Africa.
- (7) *Anopheles (Myzomyia) rossi*. India.

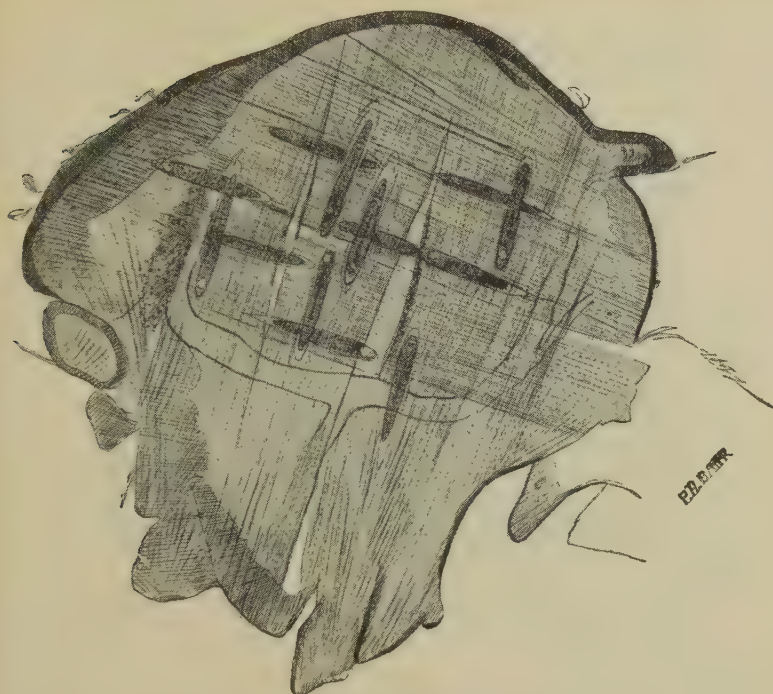


Fig. 276.—Section of thoracic muscles of *Aedes variegatus*: fourth day after infection. (Orig.)

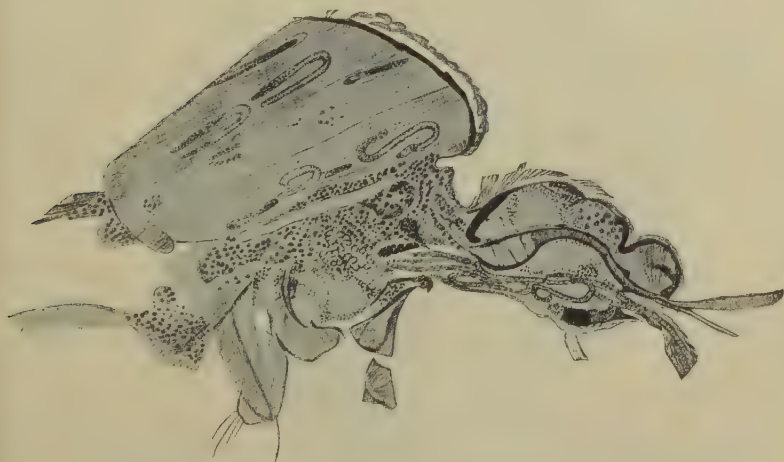


Fig 277.—Section of *Aedes variegatus*, showing filariæ in thorax, on tenth day of development, travelling forwards into proboscis. (Orig.)

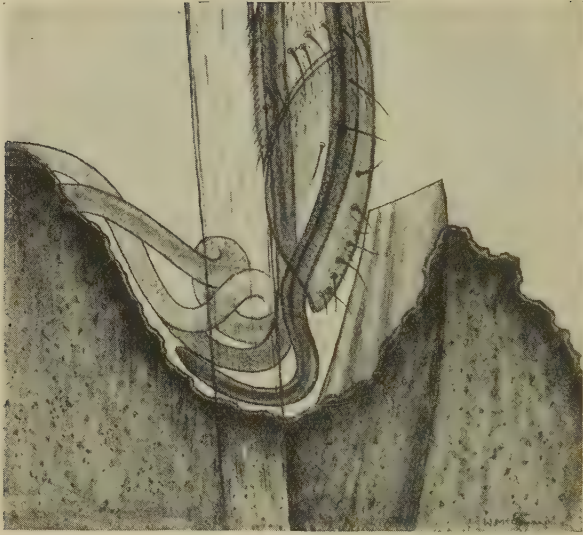


Fig. 278.—Larval filariæ (*Dirofilaria immitis*) leaving proboscis of mosquito and burrowing through the skin. (Partly diagrammatic, after Fülleborn.)

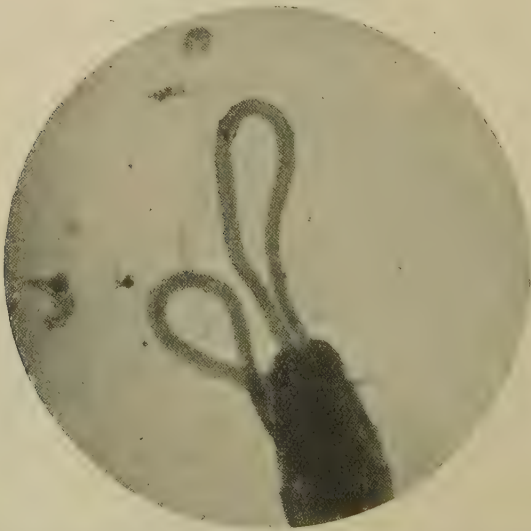


Fig. 279.—Larval filaria emerging from proboscis of *Aedes variegatus*. (Orig.)

(8) *Anopheles gambiae (costalis)*. West Africa.

(9) *Anopheles algeriensis*. Tunis.

Twenty-two species have been listed in which partial development has been observed.

Brug has recently described as *Filaria malayi* a microfilaria which differs from that of *F. bancrofti* in the position of the anal pore and the arrangement of the nuclei in the tail. It is said not to undergo development in *Culex fatigans*,

FILARIA OZZARDI (Manson, 1897)

Habitat.—The mesentery of man.

Geographical distribution.—West Indies and South America.

Characters.—Manson first discovered the embryos of this species in the blood of aboriginal Carib Indians sent by Ozzard of British Guiana. In shape and size the embryos closely resembled those of *Acanthocheilonema perstans*; they were sheathless, but they had sharp tails, in contradistinction to the blunted extremity of that species. They observed no periodicity, and were present in the blood-stream both by day and by night. It was at first thought that similar embryos from natives of St. Vincent (Newsam) represented a different species, distinguished by Manson as *F. demarquayi*, but it is now generally recognized that only one species exists. *F. ozzardi* has been recorded from the West Indies and South America, while Manson found a similar microfilaria in the blood of an aboriginal of New Guinea. This has been confirmed by Seligman. Some 25-30 per cent. of the inhabitants of the Northern Provinces of the Argentine Republic are infected with a similar microfilaria (Biglieri and Araoz). In British Guiana the microfilaria of *F. ozzardi* is nearly always found in the blood in conjunction with the microfilaria of *A. perstans*. It has been suggested by some that these embryos are dimorphic.

The parental forms of this microfilaria were first found by Daniels at the autopsy of two Demerara Indians; later, Galgey found five adult females in the omental tissues of a native of St. Lucia. In Daniels' cases they were situated in the mesentery and the visceral fat. He stated that a male which he examined measured about 32 mm. in length; the tail was much coiled, and carried at least one spicule. The female is about 65-81 mm. long and 0.210 to 0.25 mm. broad. The head is somewhat club-shaped and bears no papillæ. The vulva is situated 0.76 mm. from the anterior extremity, the anus 0.23 mm. from the tip of the tail. The embryos measure 173-240 μ in length by 4-5 μ in diameter. As far as is known, this filaria is not pathogenic. The microfilaria is non-periodic. (Plate XXX, Fig. 4, facing p. 535.) The intermediate host has not been ascertained.

As the adult form in this species is imperfectly known, this worm has been retained in the genus *Filaria*.

LOA LOA (Guyot, 1778)

Habitat.—The connective tissues.

Geographical distribution.—*L. loa* is widely distributed throughout tropical West Africa. It is a parasite of man, as far as is known. A closely allied parasite has been described by Treadgold in *Papio cynocephalus* and named *L. papionis*.

Characters.—The adult male measures 30-34 mm. in length, and presents a maximum breadth of 0.350-0.430 mm. in the anterior part of the body. (Fig. 280.) The posterior part tapers gradually towards the tail. The measurements of the adult female have not been satisfactorily determined; the specimens so far examined extracted from under the skin or from about the

eyes of patients, varied greatly in length from 20 to 70 mm. The breadth is about 0.5 mm. (Fig. 281.)

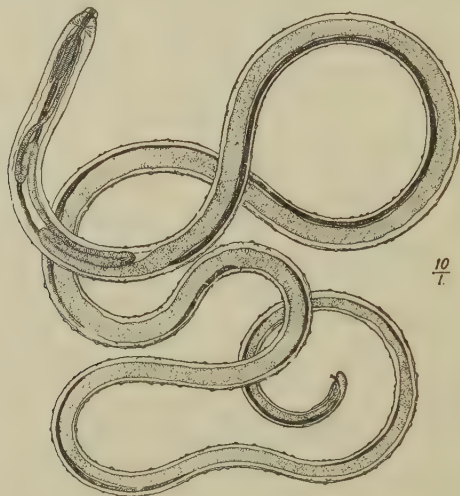


Fig. 280.—*L. loa*, male. (Partly after Looss.)

L. loa is especially characterized among the nematodes of man by the presence of numerous rounded, smooth, translucent protuberances of the

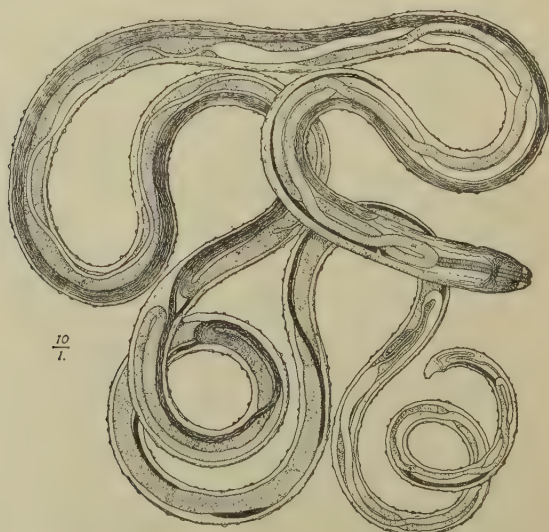


Fig. 281.—*L. loa*, female. (Partly after Looss.)

cuticle, 12–16 μ in diameter, and rising 9–11 μ above the general surface. These chitinous bosses vary greatly in number and arrangement in different specimens, and are, as a rule, more numerous in the female. Their distribution is very irregular. In the male they are wanting at the extremities, beginning about 1.5–2.5 mm. from the mouth and tail-tip respectively. In the female they usually extend to the posterior extremity, and may also be found on the cephalic end.

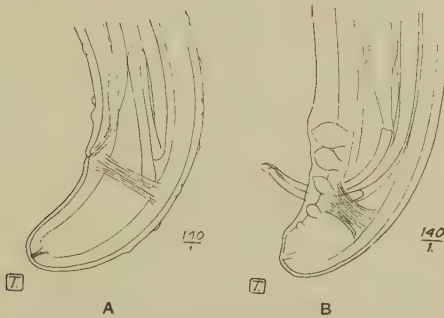


Fig. 282.—Posterior extremity of *L. loa*, (A) female, (B) male. (After Looss.)

The body is filiform, cylindrical, whitish, semitransparent. Anteriorly it tapers somewhat abruptly to the mouth, which is terminal, small, simple, unarmed, and apparently destitute of papillæ. There is no distinctly marked neck, but there is a sort of shoulder about 0.15 mm. from the mouth, and at about this level are two small papillæ, one corresponding to the dorsal, the other to the ventral median line.

The alimentary tube begins at the oral cavity, which is funnel-shaped and surrounded by a strong muscular mass. It consists of a slender œso-

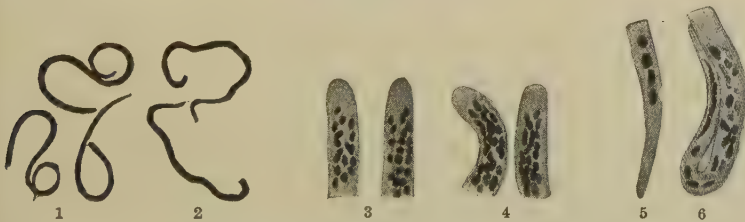


Fig. 283.—Distinguishing features of *microfilaria bancrofti* and *microfilaria loa* in stained specimens.

Attitudes (1) of *microfilaria bancrofti*, (2) of *microfilaria loa*. Heads (3) of *microfilaria bancrofti*, (4) of *microfilaria loa*. Tails (5) of *microfilaria bancrofti*, (6) of *microfilaria loa*.

phagus without bulb, of an intestine attaining a width of about 65 μ towards the middle of the body, and of a short, attenuated rectum.

The tail of the *male* is slightly curved ventrally and provided with two lateral expansions of the cuticle (0.7 mm. long by 0.029 mm. broad), situated nearer the ventral than the dorsal surface. In the middle of the ventral surface, between the lateral alæ, and about 0.08 mm. from the tail-tip, is the opening

of the ano-genital orifice, from which two unequal spicules may be seen protruding; the longer measures $123-176\ \mu$, the shorter $88-113\ \mu$; the opening is surrounded by thick labia. On either side, and somewhat asymmetrically placed, are four large globular and pedunculated papillæ closely approximated and decreasing in size antero-posteriorly. Farther back, and nearer to the



Fig. 284.—Development of *Loa loa* in chrysops.
(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med.")

1, Larva, 24 hours old; 2, fourth day (length $390\ \mu$); 3, fifth day;
4 seventh day (length $1.5\ \text{mm.}$); 5, tenth day (length $2\ \text{mm.}$,
breadth $0.025\ \text{mm.}$).

middle line, is a fifth symmetrical pair of very small, conical, postanal papillæ with broad base and acuminate point. (Fig. 282, B.)

The posterior extremity of the *female* is straight, attenuated, and broadly rounded off. The vulva forms a small eminence about $2.5\ \text{mm.}$ from the anterior extremity. The vagina, $9\ \text{mm.}$ long and $95\ \mu$ wide, branches off into two long tubes extending almost throughout the entire length of the body. (Fig. 282, A.) These tubes, the narrow ends of which are the ovaria, con-

tain eggs in all stages of development. The mode of reproduction is ovoviviparous, the embryos developing within the egg envelope and uncoiling themselves on expulsion from the vagina in a similar manner to that of *microfilaria bancrofti*.

The embryo.—*Microfilaria loa* (or, as it is sometimes called, *microfilaria diurna*) is very similar in size ($298\ \mu$ by $7.5\ \mu$) and structure to that of *microfilaria bancrofti*. Although in the fresh liquid blood it is practically impossible to distinguish, with the microscope alone, the living microfilariae of the two species, in dried and stained films certain more or less pronounced differences can be made out. (1) In such preparations *microfilaria bancrofti* is usually disposed in sweeping curves (Fig. 283, 1); *microfilaria loa*, on the other hand, assumes a stiff, ungraceful, almost angular attitude (Fig. 283, 2). (2) The tail end of *microfilaria loa* is often disposed in a series of sharp flexures, giving

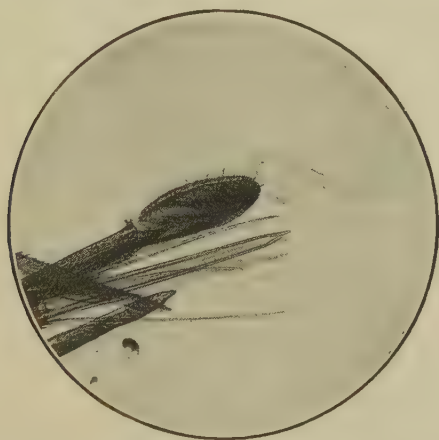


Fig. 285.—Development of *L. loa* in *Chrysops silacea*, showing several mature larvæ at tip of labella.

(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med. and Hyg.")

it in some instances a corkscrew-like appearance, the extreme tip being always sharply flexed (Fig. 283, c). (3) The nuclei of the central column of cells of *microfilaria loa* are larger and stain less deeply than those of *microfilaria bancrofti*, and, as a rule, the cephalic end of the column is more abruptly terminated in the former. Although in most slides one or two specimens may be hard to diagnose, on the average of a series of preparations the foregoing distinctions are recognizable. Fülleborn, by special staining methods, points out various minor differences (Fig. 273), among which the large genital cell is a marked feature.

Sharp (1923) has pointed out that certain differential characteristics may be distinguished in the living embryos by staining with methylene-blue. A drop of blood is placed upon a drop of this stain, 1 : 5,000; if the embryo is that of *L. loa* it begins to take up the stain in ten minutes, while in the case of *microfilaria bancrofti* absorption is much slower and the stain picks out the excretory pore.

The embryo may not appear in the peripheral blood-stream of a patient infected with *L. loa* in some instances, till a period of six, or even seven, years has elapsed.

Life-history.—Development proceeds, in much the same manner as in the case of *Filaria bancrofti*, in the body of certain day-biting, blood-sucking flies, "mangrove flies," *Chrysops silacea* and *C. dimidiata*. On entering the stomach of these insects the embryo casts its sheath within a period of three hours and, piercing the stomach-wall, enters the thoracic muscles, the connective tissue and fat-body (Stevenson) of the thorax and head, but principally that of the abdomen. Larval development is complete in ten days. In three days the developing filaria has broadened out and has assumed a torpedo-shape; shortly afterwards the intestinal canal becomes formed. On the fourth and fifth days the short, squat form becomes lengthened out to 0·8 or 1 mm.; on the sixth the corkscrew appearance is replaced by gentle curves, and the first ecdysis takes place; the sharp-pointed tail is then replaced by a gently-rounded and trilobed extremity. The larva continues to grow so that by the tenth day it measures 2 mm. in length by 0·025 mm. in breadth. (Fig. 284.) The larvæ have now congregated in the head in large numbers, the majority being found at the root of the proboscis, and make their way out to the surface of the skin of the intermediary host, breaking through the proboscis sheath when the infected fly feeds. (Fig. 285.) The flies themselves can remain infective for five or six days. The Connals have found that in Calabar 3·5 per cent. of the wild-caught flies are naturally infected with *Loa loa*.

ACANTHOCEILONEMA PERSTANS (Manson, 1891), Railliet, Henry and Langeron, 1912

The adult worm was discovered by Daniels in Demerara Indians, and subsequently identified by Manson. The embryo, or microfilaria, was first discovered in the blood by Manson in 1891.

Habitat.—The mesentery of man.

Geographical distribution.—The embryo of this parasite is very common in the blood of the natives of large districts in tropical Africa, and apparently occurs also in the chimpanzee. It has been recorded from the Congo, Nigeria, the Gold and Ivory Coasts, and in Sierra Leone. It is common in northern Rhodesia and in Uganda, where in some districts it may be found in 90 per cent. of the population; it probably also occurs in New Guinea.

It is frequently encountered in the blood of Europeans who have resided in Central Africa. Sometimes it occurs along with microfilaria loa and microfilaria bancrofti, and in British Guiana with microfilaria ozzardi, in the same individual.

The South American form may very well be a distinct species, but as the microfilariae are morphologically similar and the adult parasites are insufficiently known, at present it is thought advisable to regard them as one and the same species. (Map. VI, facing p. 536.)

Characters.—*A. perstans* is, like *F. bancrofti*, a long, cylindrical, filiform nematode. The body is smooth, without markings; the mouth simple and unarmed. The tail in both sexes is peculiar and characteristic; it is incurvated, and the chitinous covering at the extreme tip is split up as it were into two minute triangular appendages, giving it a mitred appearance. The male is smaller than the female; it measures 45 mm. in length by 0·06 mm. in breadth. The diameter of the head is 0·04 mm. Close to the opening of

the cloaca there are four pairs of preanal and one pair of postanal papillæ. Two unequal spicules may be seen protruding from the cloaca. (Fig. 286.) The adult *female* measures 70 to 80 mm. in length by 0.12 mm. in breadth. The head is club-shaped and measures 0.07 mm. in diameter. The genital pore opens at 1.2 mm. (Chesterman) from the head. The anus opens at the apex of a papilla situated in the concavity of the curve formed by the tail. The diameter of the tail just before termination is 0.02 mm.

The adult worms are sometimes found in numbers in the mesentery and in the perirenal and retroperitoneal tissues, and in the pericardium. According to Brumpt, they generally occur singly, and cause no reaction of the surrounding tissues. Chesterman has discovered the adult female in a small cyst, the size of a peanut-pod, overlying the brachial artery. The cyst was full of serous fluid and resembled that produced by *O. volvulus*.

The embryo.—*Microfilaria perstans* observes no periodicity, being present in the blood both by day and by night, but its numbers at different times may vary considerably. In this respect it resembles *microfilaria ozzardi*. Its special seat of selection is not the peripheral blood, but that of the heart, lungs, aorta and other large vessels. It has not been found in the spleen and only rarely in the liver and pancreas. The embryo in the blood

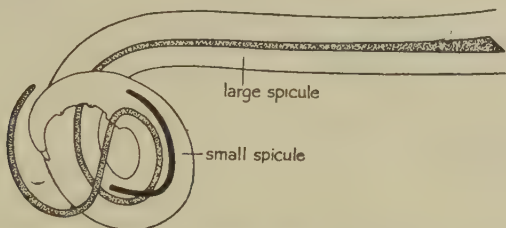


Fig. 286.—Tail of *Acanthocheilonema perstans*, showing two unequal spicules and papillæ. (After Leiper, in Brumpt's "*Précis de Parasitologie*.")

measures on an average $200\ \mu$ by $4.5\ \mu$; but, as it possesses in a remarkable degree the power to elongate and to shorten itself, these measurements do not always apply. (Plate XXX, 2, facing p. 535.) Brumpt and others recognize a long and a short form, the latter being $90\text{--}110\ \mu$ in length by $4\ \mu$ in breadth. It is manifestly much smaller than the microfilaria of *F. bancrofti* or of *Loa loa*, and is further distinguished from them by the entire absence of a sheath and by the characters of its caudal end, which is invariably truncated and abruptly rounded off. The taper which terminates in the tail extends through quite two-thirds of the entire length of the embryo. The V-spot is about 0.03 mm. from the cephalic extremity. There is no marked tail-spot. No hooked cephalic prepucce can be made out. According to Fülleborn, no red staining "granular mass" can be demonstrated. Its movements also differ from those of *microfilaria bancrofti*, for it not only wriggles about, just as that parasite does, but indulges in long excursions through the blood, moving freely all over the slide—locomoting, in fact, very much in the same way as the other species do in the insect's stomach after they have cast their sheaths.

Life-history.—Dyce Sharp has worked out the cycle of development of *A. perstans* in a small midge—*Culicoides austeni*, in the Cameroons. The embryos when ingested undergo development in the wing muscles in the

same manner as *F. bancrofti*. Within six to nine days the larval filariæ are ripe for emergence in the proboscis where they generally appear in pairs. Previous to emergence there occurs a globular expansion of the labrum which eventually collapses and gives exit to the filariæ (Sharp). (Fig. 287.) They measure at that time 0.7 mm. in length. About 7 per cent. of wild flies are naturally infected. Considerable difficulty is experienced in keeping these small insects alive in confinement, unless they receive a second feed of blood.

Pathogenesis.—*A. perstans* appears to be particularly harmless to its host. It is surprising that in its wanderings in the mesentery it does not



Fig. 287.—Larva of *Acanthocheilonema perstans* in proboscis of *Culicoides austeni*. (Dyce Sharp. Microphoto : Dr. A. C. Stevenson.)

give rise to greater disturbance; possibly transient abdominal pains in the region of the gall-bladder may be attributed to its presence. As already related it may form, occasionally, subcutaneous cysts.

ONCHOCERCA VOLVULUS (Leuckart, 1893), Railliet and Henry, 1910

Habitat.—The subcutaneous tissues of man, especially the intercostal spaces, the axilla and popliteal space, and suboccipital region.

Geographical distribution.—West Coast of Africa and Guatemala.

Characters.—The body is white, filiform, and tapering at both ends. The head is rounded, with a diameter of 0.04 mm., and the cuticle is marked by transverse ridges.

The male is 20–32 mm. in length by 0.2 mm. in breadth. The alimentary canal is straight, and ends in a subterminal anus. The tail terminates in a single spiral, and is bulbous at the tip. There are two pairs of preanal, two pairs of postanal, and an intermediate large papilla. Two unequal spicules, measuring 0.082 and 0.177 mm. respectively, may be seen protruding from the cloaca (Fig. 288).

The female is of very considerable length, measuring 60–70 cm. by 0.4 mm., but more recent measurements are considerably smaller, giving a length of 35–40 cm. (Schäfer).

The head is rounded and truncated; it measures 0.04 mm. in diameter. The vulva is situated 0.85 mm. from the anterior extremity, and the tail is

curved. The cuticular striations are said to be not so distinct as in the male. *O. volvulus* is ovoviviparous. The egg possesses a peculiar striated shell, and measures 30–50 μ in diameter. At least four males and two females are present in every tumour.

The embryo is sheathless, and measures 300 μ in length by 8 μ in breadth as a general rule; though in the fluid of the cyst-cavity in the surrounding skin, two types, a larger and a smaller one, are present (Blacklock). The body tapers from about the last fifth of its length, and ends in a sharply-pointed recurved tail. (Fig. 289.)

At about the anterior fifth of the body there is a gap in the central column of cell (V-spot). There is a slight thickening behind the cephalic cone at the commencement of the nuclear column. The embryo is non-periodic in

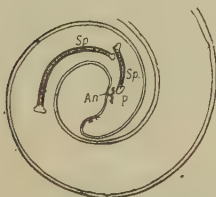


Fig. 288.—Caudal extremity of *Onchocerca volvulus*, ♂. (After Brumpt.)

Sp., Spicules; An., anus;
p., papillæ.

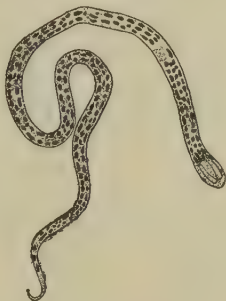


Fig. 289.—Embryo of *Onchocerca volvulus*.
× 500. (After Dyce Sharp.)

habit, and has been found in the blood (Fülleborn), in the femoral, inguinal, and cervical lymph-glands, and in the expressed juice of tumours.

According to Macfie and Corson, these embryos are found in the skin of widely separated portions of the body of apparently healthy natives (34 per cent.) of the Gold Coast.

Life-history.—Blacklock, working in Sierra Leone, where in certain parts 45 per cent. of the inhabitants harbour embryos of *O. volvulus* in their skins, often unassociated with any pathological condition, has traced the development of this filaria in the “buffalo-gnat”—*Simulium damnosum*. The fly abstracts the embryo from the deeper layers of the skin in the vicinity of the nodule. The embryos enter the stomach and piercing its walls come to lie amongst the thoracic muscles where they undergo a development similar to that of *F. bancrofti* in the mosquito. During their growth one or more ecdyses probably take place (Blacklock). After seven days the larval filaria measures 657 μ . Development has been traced up to the tenth day and, probably, the larva escapes from the proboscis as in the case of other filariæ. *S. damnosum* bites from 6 a.m. to 6 p.m. Dissection of wild-caught simulum flies showed that 2.6 per cent. were naturally infected. Dyce Sharp has shown that this simulum has a selective action in abstracting the embryos of *O. volvulus* from the blood. By scraping the skin with its prestomal teeth it sucks up the serum from the wound and with it the filarial embryos.

Brumpt has separated the South American form of *O. volvulus* under the name of *O. cæcutiens* Brumpt, 1919, but this is doubtfully a valid species. It is said to differ from *volvulus* in the size and shape of the papillæ in the male,

in the size of the spicules, and in its association with eye and skin lesions (see p. 573).

On account of its peculiar distribution at high altitudes in the Andes, it has been suggested on epidemiological grounds that the intermediary host in this instance is also a simulum.



Fig. 290.—*Agamofilaria streptocerca* embryo, showing characteristic curvature of tail. $\times 200$. (Dyce Sharp.)

Under the name of *Agamofilaria streptocerca*, Macfie has described a sheathless microfilaria as being commonly found in the corium of the skin, but not in the bloodstream, of natives of the Gold Coast, for he found it in 22 out of 50 men examined at Accra. The adult nematodes are as yet unknown. The embryo measures $215\ \mu$ in length, and can be distinguished, according to Dyce Sharp, by the "walking-stick handle" appearance of the tail extremity. Recently experiences have shown that this filaria has a wide distribution and is common in the Cameroons. The arrangement of the nuclei in the head and four rounded ones in the tail are distinctive and afford an index of differentiation from the embryo of *O. volvulus* and *A. perstans*. The insect vector is at present unknown. (Fig. 290.)

DRACUNCULUS MEDINENSIS (Linn., 1758)

GUINEA-WORM.

Habitat.—The subcutaneous tissue of man, especially of the leg, arm, and back. Its occurrence in the ox, horse, dog, wild-cat, jackal, and leopard is now regarded as accidental.



Fig. 291.—*Dracunculus medinensis*. One-third nat. size.

Geographical distribution.—*D. medinensis* is a common parasite of man in India and Africa apparently, and has been imported into the West Indies and South America. In Guiana and Brazil it has now become endemic.



Fig. 292. — Anterior extremity of *Dracunculus medinensis*. $\times 8$. (After Leuckart.)



Fig. 293.—Transverse section of *D. medinensis*. (After Leuckart.)

Characters (Figs. 291, 292).—The *female* is reputed to attain, in some instances, enormous dimensions; it is probable, however, that worms of 5 ft. or 6 ft. in length owe their size to errors of observation—two worms, or their fragments, having been regarded as one. According to Ewart, in forty carefully measured specimens the smallest was about 32.5 cm., the largest 1 m. 20 cm. in length; 90 cm. is probably an average length. The diameter of the worm is about 1.5–1.7 mm. The body is cylindrical, milky-white, smooth, and without markings. The tip of the tail comes to a point and is abruptly bent, thus forming a sort of blunted hook. The head end is rounded off, terminating in what is known as the cephalic shield. The mouth is triangular, very small, and surrounded by six papillæ—two large and four small. The alimentary canal is relatively small, being compressed and thrust to one side by the uterus; in the mature worm it is probably cæcal, for it has not been traced to an anus. Nearly the whole of the worm is occupied by the uterus, which is packed from end to end with coiled-up embryos. (Fig. 293.) The vagina also may be lacking. According to Looss, the uterine tubes (he states, contrary to Leuckart, that there are two) open into the posterior part of the œsophagus by a common duct, the œsophagus prolapsing through the mouth at the time of parturition and being subsequently withdrawn. Leiper, however, has shown that the worm discharges its young by a prolapse of the uterus, as described by Manson, and that the extrusion does not occur through the mouth, as suggested by Looss and Manson, but by a rupture just outside the circumoral ring of papillæ, possibly the vagina.

Nothing definite is known of the *male* worm. According to Polak, the Persians have long known the male to be a smaller worm, 7–10 cm. long. They also stated that at times as many as twenty of these small worms might be found coiled round a female specimen. A shorter (4 cm.) worm is described and has been regarded as the male, attached to the larger female worm within the subperitoneal connective tissue. Daniels, at the post-mortem of a monkey experimentally infected by Leiper six months previously, found three immature females (30 cm. long), and two remarkably small males (22 mm.) which were obtained one from the psoas muscle and the other from the connective tissue behind the œsophagus.

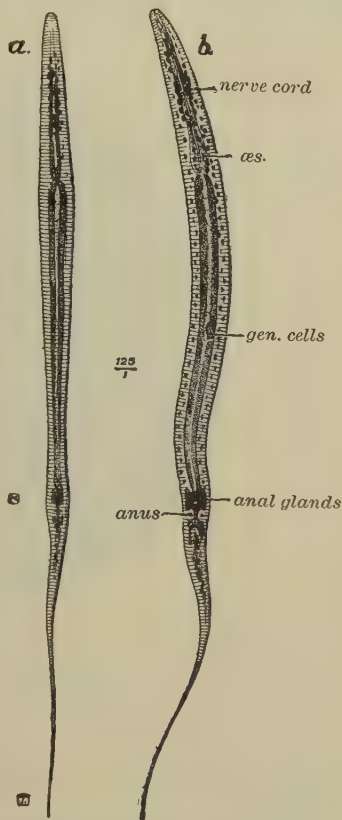


Fig. 294.—Embryos of *D. medienensis*. $\times 150$.

a, Side view; b (after Looss), front view.

The embryos (Fig. 294) measure 650–750 μ long by 17 μ broad. According to Looss, they are flattened, not cylindrical. They are provided with a long, slender tail, a rounded head, an easily distinguishable alimentary canal, a rudimentary anus, and a bulbous oesophagus. The cuticle is transversely striated. Two peculiar glandular organs are situated in the root of the tail.

The embryos, in swimming, move by a sort of side-to-side lashing of the tail and tadpole-like motion of the body. The movements are intermittent, sudden short swims alternating with brief pauses. When progressing, the greater transverse axis of the body is perpendicular to the plane travelled over.

In clean water the embryo remains alive for six days; in muddy water

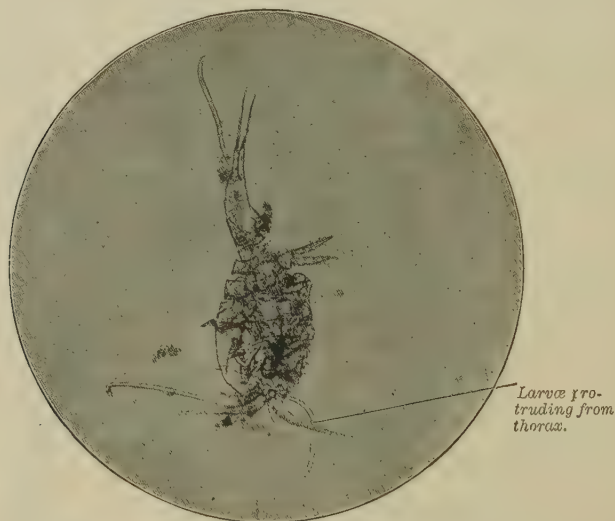


Fig. 295.—Embryos of *D. medinensis* in body-cavity of a cyclops.
(Photo: Mr. Andrew Pringle.)

The cyclops has been slightly compressed so as to force out some of the worms, which can be seen escaping from ruptures at the head and tail.

or in moist earth it will live from two to three weeks. If slowly desiccated it does not die, but may be resuscitated by being again placed in a little water.

Life-history.—If *dracunculus* embryos are placed together with *Cyclops quadricornis*, or allied species (*C. strenuus*, *C. viridis*, and *C. bicuspidatus*), in a watch-glass, after a few hours the embryos will have been ingested by the cyclops (Fig. 295), where they can be seen moving about, coiling and uncoiling themselves, with considerable activity. As many as fifteen or twenty larvæ may be counted in each crustacean, which, unless the infection is excessive, seems in no way inconvenienced. After a time the embryos so transferred undergo a metamorphosis. They cast their skins two or three times, get rid of their long, swimming tails, acquire a cylindrical shape, and ultimately, along

with increased size, develop a tripartite arrangement of the extreme posterior end, as in *Filaria bancrofti* and *Loa loa*. The rate of development varies according to the temperature; usually it takes four to six weeks. This larva is 1 mm. in length, and at this stage it is ingested by man and completes its development in the connective tissues.

According to Liston, 38.6 per cent. of the cyclops in some Indian villages are infected; while Chatton in Dahomey records a much higher figure. The latter has suggested that the same species of *Cyclops* does not necessarily form the most suitable intermediary host in the various countries in which the guinea-worm is endemic. In Tunisia the appropriate species appears to be *C. viridis*.

ACANTHOCEPHALA

The Acanthocephala are nema helminthes unprovided with an alimentary canal. The sexes are distinct, and the larval stages are passed in insects and crustacea.

Two species, *Gigantorhynchus gigas* (Goeze, 1782) and *G. moniliformis* (Bremser, 1819), have been found parasitic in man on a few occasions. The former is normally a parasite of the pig, and is said to have occurred in the small intestine of man on the Volga; the latter is a common parasite of the rat, and has been reported in man from Italy and from Khartoum by Christopherson.

IV. MEDICAL ENTOMOLOGY

MEDICAL entomology entails a study of numerous diverse creatures included in the phylum arthropoda ; those of medical interest are found in the classes, Crustacea, Arachnida, and Insecta.

ARACHNIDA

ORDER ACARINA

The Acarina have a short abdomen which is fused with the cephalothorax to form a single structure. The larvæ have only three pairs of legs ; the eyes may be absent or very small. Respiration takes place by means of air-tubes or through the skin. The order includes, amongst others, three families, Sarcoptidæ, Demodicidæ, and Ixodidæ.

SARCOPTES SCABIEI (Linn., 1758)

ITCH-MITE

Habitat.—The skin of man. Morphologically identical species are found on all domesticated animals, as well as on foxes, wolves, and the llama. The animal sarcoptidæ can maintain a temporary existence on the human skin.

Characters (Figs. 296, 297).—The female is 0.3–0.4 mm. in length, the male 0.2 mm. The latter is provided with a penis situated at the fourth pair of legs. The sexes may be distinguished by the epimera of the second pair of hind-legs, which unite with the sexual orifice in the male, but in the female are free : the hind-leg in the male is provided with a sucker ; in the female, with a bristle. The gravid female lives in a burrow in the skin, at the entrance of which the male keeps watch. The eggs, measuring 150 μ in length by 100 μ in breadth, are laid in the burrow, 40–50 in number, and give rise in a period of three to five days to larvæ, which pass through four stages in a period of about three weeks. In the first stage the hexapod larva moults several times, becoming an octopod nymph, characterized by 12 dorsal spines. The third stage is entered about the twentieth day, when the nymphs moult and become sexual males and females, which pair off. During the fourth stage the impregnated female moults once more and develops a sexual orifice ; she then burrows into the skin and deposits the eggs. The average life of the adult parasite is four to five weeks (Munro).

Prevention and treatment of scabies.—The promiscuous use of blankets and the lack of washing facilities aid in the spread of the disease. Preparatory to treatment the patient should be well washed in a hot bath at 106° F. containing 2 oz. of washing soda. He should be instructed to immerse himself in this for twenty minutes. The body is then scrubbed well with soft soap and a scrubbing brush, the hands with a stout tooth-brush. The burrows are thus torn open and the acari removed or exposed to the parasiticide. After drying, the patient is rubbed all over with a piece of lint dipped in

3 oz. of liquor calcis sulphuratus B.P. ; it is important that a fresh solution be used for each case. If the skin is very sensitive, it may be necessary to dilute the solution at first. If this solution cannot be obtained, unguentum sulphuris, 2 oz. at a time, should be thoroughly rubbed in for at least twenty minutes. The treatment of scabies by sulphur fumigation is useless.

Mitigal (Bayer and Co.), a hydrocarbon compound containing sulphur, is less irritating and possesses no unpleasant odour. It is rubbed into the affected area for three consecutive evenings.

The Sarcoptidæ comprise other mites parasitic on beetles, birds, bats, etc. A separate family, the Tarsonemidæ, are minute, soft-bodied, transparent mites, parasitic on plants, but which may become temporary parasites on man and give rise to an intolerable itching by excretion of some venomous substance. In this family the chelicerae are pointed, the



Fig. 296. — *Sarcoptes scabiei*: ventral aspect. $\times 35$. (After Canestrini.)

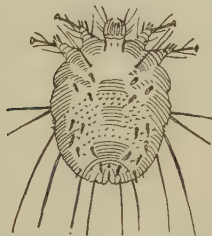


Fig. 297. — *Sarcoptes scabiei*: dorsal view. $\times 40$. (After Brumpt.)



Fig. 298. — *Leptus autumnalis*. $\times 50$. (After Hirst, "Journ. Economic Biol.")

pedipalps hardly visible, and the last two pairs of legs are placed far behind the anterior pair. *Pediculoides*, especially the species *P. ventricosus* (Fig. 178, p. 658), is parasitic on insects, and is often found in raw cotton, which has given rise to epidemics of itch among stevedores unloading cotton ships. The abdomen of the pregnant female of this species becomes swollen with eggs, like a small chigger. In it the eggs hatch and the young complete their development, to issue forth as adults (p. 658).

The family of Tyroglyphidæ, or cheese-mites, are minute, light-coloured creatures with a distinct cephalothorax; the legs are of a moderate length, often terminating in a sucker. These insects, which are found in flour, dried fruit, cheese, and copra, occasionally infect the skin of grocers who handle these substances, causing an erythema known as "grocer's itch" and, in the case of copra dealers, "copra itch." The insects are sometimes passed intact through the alimentary canal, and may appear in the stool, where they may be found on microscopic examination.

The family Trombididæ are large, bright-red creatures, known as velvet mites, predaceous on their own kind and other insects, while some are very destructive to plants. The larvæ of this family may infect the human skin,

causing very severe itching, and are known as harvest-bugs. The orange-coloured larva, *Leptus autumnalis*, 0.5 mm. in length, is produced from eggs which are deposited by the parents on the ground. (Fig. 298.) The adult form is unknown. Normally this mite is parasitic on moles and hares; it only lives for a few days on man. Inunction with oleum cajuputi, or bandaging the irritated part with material soaked in a weak solution of subacetate of lead or sulphate of copper, gives relief.

Other species of medical interest are *Trombicula akamushi*, *T. schüffneri* and *T. deliensis*, the Kedani mite, or intermediary hosts of the virus of Japanese river fever; (Figs. 299, 300.) The form which transmits the disease is the hexapod larva of a mite (*Trombicula akamushi*), and lives on the field-vole (*Microtus*), the house-rat of Formosa (*R. rattus rufescens*), and other rodents. The adult form, or *Trombicula*, is found in the soil of infected fields; it is a tiny creature 0.9 mm. in length by 0.5 mm. in breadth, is pale-



Fig. 299.—*Trombicula akamushi*: full-grown imago. $\times 35$. (After Mizajima and Okumura.)



Fig. 300.—Larva of *Trombicula akamushi*. $\times 80$. (After Hirst, "Journ. Economic Biol.")

grey or red in colour, with two rudimentary eyes and four pairs of legs; the anterior pair of legs are stout, and are carried on the anterior part of the cephalothorax parallel to the pedipalps. On the ventral surface are situated two pairs of suckers close to the genital orifice and the anus. The larva, or leptotrombicula, measures 0.4 mm. in length by 0.25 mm. in breadth, and resembles *Leptus autumnalis* in general appearance, but the legs and pedipalps are stouter, and the body, including the legs, is covered with minute plumose hairs. The cephalothorax bears a pair of eyes conspicuously red in colour. The nymph has a peculiar figure-of-eight shape, an abdominal constriction dividing the body into two parts. It measures 0.65 mm. in length, and in due season moults and becomes adult.

Harvest-bugs occur in practically every part of the world and are especially annoying in some parts of the tropics. In Surinam there is a very virulent form known as *Acarus balatus*; in New Guinea and Celebes the *Microtrombidium wichmanni*, in South America the *Microtrombidium moles-tissimum*, or "Bicho Colorado," are the best known.

DEMODEX FOLLICULORUM var. HOMINIS (Simon, 1842)

This parasite (Fig. 301) lives in the hair-follicles and sebaceous glands around the mouth and nose of man. Similar species are met with in most domestic animals, as in the case of *Sarcoptes*. These acarines are very minute, 0.3-0.4 mm. in length. The abdomen is marked off from the cephalothorax, and is elongated and transversely striated. The anal opening is situated at the junction of the cephalothorax and abdomen. The head is provided with a prominent rostrum—there are no vestiges of eyes; the mouth is adapted for sucking, and is provided with various rudimentary appendages. The cephalothorax has four pairs of very short and stumpy legs with terminal rudimentary claws. These parasites live with their heads inserted deeply into a hair-follicle. In order to demonstrate them, one should express the sebum from the mouths of the sebaceous glands or comedones, and examine under a microscope in a drop of oil or xylol. If the condenser is shut down, one can distinguish the different larval stages.

Life-history and pathogenesis.—The female lays heart-shaped eggs, 60-80 μ long and 40-50 μ broad, which on hatching give rise to hexapod larvæ; after moulting several times these become sexually mature. All stages of development are passed within the follicles, but the mature parasites are believed to migrate over the skin. As regards their pathogenic rôle, they are responsible for inflammation of the eyelids when they occur in the Meibomian glands.



Fig. 301.
Demodex
folliculo-
rum.
 $\times 100.$
(After
Brumpt.)

Family Ixodidæ

The Ticks are cosmopolitan in their distribution, and are interesting as carriers of various diseases. With the exception of *Argas* and *Ornithodoros*, they rarely voluntarily attack man in the adult state. Ticks are always visible to the naked eye, and the females are invariably larger than the males; in some species the fully engorged females may measure nearly half-an-inch in length.

The cephalothorax and abdomen are fused to form a single structure; the body is covered with a leathery cuticle, which in the hard ticks (Ixodinæ) is partly chitinous, forming a dorsal shield, or scutum. (Figs. 302-307.) The mouth-parts are characteristic, and are borne by the capitulum, which may project anteriorly or be embedded in the cephalothorax, as in *Argas* (Fig. 308) and *Ornithodoros* (soft ticks—Argentinæ). From the dorsal surface of the rostrum two chelicerae pass forward, one on each side of the middle line, provided terminally with hooks. On the ventral surface is situated a symmetrical hypostome, armed with files of strongly recurved teeth; this aids the chelicerae in boring through the skin. The whole of these structures is covered on the dorsal aspect by a sheath, an expansion of the capitulum. Laterally placed to the chelicerae are two stout, jointed pedipalps, which are thought to form an adjustable sheath for the delicate mouth-parts, and are frequently hollowed on their inner surface for this purpose. During haustellation these pedipalps are deflected. On the ventral surface of the body are four pairs of legs, each consisting of six segments terminating in a pair of claws and, in some cases, a membranous plate, or pulvillus. A curious organ, known as Haller's organ, olfactory in function, is found in the cuticle of the tarsus or terminal joint of the first pair of legs. The genital pore, in both sexes, is situated on the

ventral surface behind the capitulum. Posterior to it, in the median line, lies the anus. The spiracles, or breathing openings, lie behind the coxæ, or basal joint, of either the third or fourth pair of legs. The mouth is situated

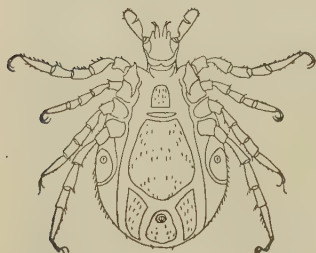


Fig. 302.—*Ixodes ricinus*.
(After Nuttall.)

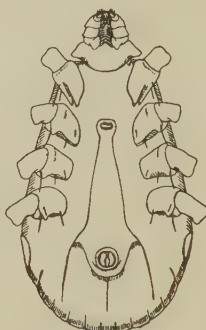


Fig. 303.—*Rhipicephalus sanguineus*.
(After Nuttall.)

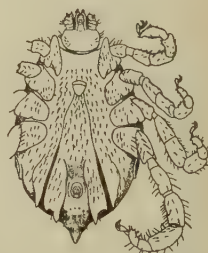


Fig. 304.—*Boophilus decoloratus*. (After Nuttall.)

between the chelicerae and the hypostome, and leads into a pharynx, a slender oesophagus, and a large stomach provided with cæca. The large salivary glands extend throughout the length of the body and open near the base of the hypostome; their secretion is in some cases very irritating, and may possibly cause a peculiar paralysis. (See p. 226.)

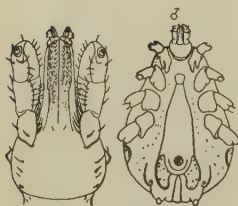


Fig. 305.—*Hyalomma ægyptum*. (After Nuttall.)



Fig. 306.—*Amblyomma*.
(After Nuttall.)



Fig. 307.—*Ap- onomma*. (After Nuttall.)

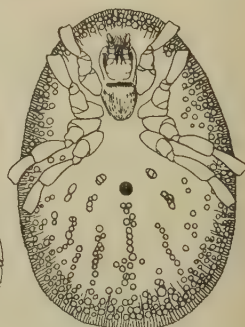


Fig. 308.—*Argas*.
(After Nuttall.)

The excretory organs are represented by two long Malpighian tubules which open into the hindgut; these are supplemented by coxal glands which open on to the coxæ. Eyes, when present, are situated as minute spots on the edge of the scutum, or on the supra-coxal folds; there may be two or even three pairs.

Life-history.—After impregnation the female tick attaches herself to her host. Becoming enormously distended with its blood, she drops off and

secretes herself in some convenient hiding-place where she deposits her eggs, which are small, yellowish grains, amounting in some cases to thousands. Oviposition begins from two to ten days after the host has been quitted, and goes on for several days. In due course (two or three weeks under favourable conditions) the eggs are hatched. The larvæ look like minute moving grains of sand; they are characterized by having only three pairs of legs, no stigmata, and no sexual orifice. A suitable opportunity presenting, the larva attaches itself to a vertebrate host. After a period of growth, it goes through a first moult (ecdysis), and emerges from its larval skin as a *nympha*, provided with eight legs instead of six, and with a pair of large stigmata placed one on each side of the body, behind the fourth pair of legs. After a second period of growth and a second moult, it becomes sexually mature. In some species, as in the case of *Margaropus bovis*, the metamorphosis from larva to nymph, and from nymph to imago, takes place upon the same host, the parasite remaining attached during the process. In other species, as in the case of *Hæmaphysalis leachi*, the tick, before each moult, drops off as soon as it ceases feeding, and in consequence has to find a host three times during its life, instead of once. Having reached maturity, the sexes unite. After fertilization the male dies, but the female proceeds to engorge herself with blood for the development of her ova.

On account of the difficulty of finding an appropriate host, ticks at all stages are endowed with a phenomenal capacity for fasting. Megnin found *Argas persicus* alive after a fast of four years' duration.

Ticks are referable to two subfamilies, the Ixodinæ and Argantinæ, differing both in structure and in life-habits.

The species of interest to the human pathologist are *Ornithodoros moubata*, *O. savignyi*, *O. lahorensis*, *O. tholozani*, *O. talajé*, *O. venezuelensis*, and *Dermacentor venustus*, the first two being the transmitters of the spirochæte of African relapsing fever; the third and fourth, possibly, of the spirochæte of the Persian form; the sixth, of relapsing fever of South America; while the last carries the germ of Rocky Mountain fever.

ORNITHODORUS MOUBATA (Murray, 1884). (See Plate XI, 3, facing p. 168.)

Geographical distribution.—This species is widely distributed in Africa, from Uganda and Somaliland in the east, and Congo and Angola in the west, to Namaqualand and the Transvaal in the south.

Characters.—The body is rotund and oval in outline; the colour, when the tick is alive, is greenish brown. The integument is hard, leathery, covered with close-set shining granules or tubercles, and marked both above and below with symmetrically-arranged grooves. The females may attain about 8 mm. in length by 6 to 7 mm. in breadth; they moult frequently.

In habit *Ornithodoros moubata* resembles the common bed-bug. It lives in the huts of the natives, hiding during the day in cracks in the walls and floors, or in the thatched roofs, and moving about actively during the night in search of nourishment. It attacks both man and beast. It feeds slowly, and would be unable to get much blood from any but a sleeping person. It deposits its eggs in batches of 50, 70, or 100. Dissection has shown that only a few eggs mature at a time. The fertility of the female is favoured by liberal feeding. She lays batches of eggs after each feed, but does not continue to moult. The eggs hatch in about twenty days. In this tick the larval stage is practically omitted. About seven days after oviposition the hexapod larva

can be seen to be forming within the translucent egg-shell. About the thirteenth day the egg-shell splits, and about the same time the larval skin splits also, and the *eight-legged nymph* throws off simultaneously both the egg-shell and its larval skin. There are several nymphal stages. The largest nymphs may equal adults in size, and show a punctiform mark where the sexual orifice is situated in the adult.

An interesting feature, and one perhaps having a bearing on the etiology of tick-transmitted diseases, pointing as it does to a channel by which the eggs may receive a germ ingested by the parent, concerns certain cells in the stomach-wall. The tick, while feeding, from time to time expels per anum a whitish material. This excretion is derived partly from the Malpighian tubes, and partly from the cells alluded to. In the stomach-wall, nourished by the imbibed blood, these cells elongate towards the cavity of the ventricle; the other end, smaller and becoming clavate, splits and emits the elaborated nutriment into the general body-cavity, where it mixes with the blood of the tick. The cell then, becoming globular, drops into the lumen of the stomach, constituting part of the white excretion expelled per anum. One can readily understand how, by the former route, a parasite could reach the tissues of the tick, including the ovaries.

O. moubata is especially common along the routes of travel. The rest-houses are always the most infested. The ticks are frequently carried long distances in mats or bedding, or in porters' loads which have been piled for safety in the rest-huts at night.

The natives of some places, and also the Boers, protect themselves by plastering their huts, both floors and walls, with mud and cow-dung. The huts are also frequently smoked in order to drive the ticks from the thatch. A most valuable remedy for immediate use is the powder of the pyrethrum flower, which should be dusted between the sheets of the bed. Some protection may be obtained by keeping a lamp alight by the bedside throughout the night.

In certain parts of Africa the distribution of *O. moubata* is overlapped by that of a closely allied species, *O. savignyi*, which is more diurnal in its habits and seems to have a predilection for market-places, cattle-stands, etc. *O. savignyi* differs from *O. moubata* in being provided with eyes, in having larger processes on the legs and a more minutely pitted dorsal surface. *O. savignyi* has been recorded from Egypt, Nubia, Abyssinia, Somaliland, British East Africa, etc., as well as from southern Asia. Its bite is dreaded by the natives.

ORNITHODORUS LAHORENSIS (Neumann, 1908)

In the nymphal state this tick lives on sheep in Central Asia. The adult lives in cracks and crevices in native houses and walls, in Persia and northern India, and emerges at night to bite man. This species has been suspected of carrying relapsing fever in Persia, but the evidence is not very conclusive.

ORNITHODORUS THOLOZANI (Laboulbène and Megnin, 1882)

A widely spread species in Persia and India, where it infects poultry and sheep-runs, and commonly attacks man. Called the "Persian bug," it has often been suspected of transmitting *T. persicum*, though experiments undertaken in Quetta on this point (Browse) were unsuccessful.

ORNITHODORUS TALAJÉ (Guérin-Meneville, 1849)

This tick, measuring 5-6 mm. in length, ranges from Mexico to Paraguay. It is nocturnal in its habits, hiding during the daytime in crevices of masonry and in bamboos. The larva and nymphal stages are found on rats, and occasionally, in Chile, on horses and in burrows of certain rodents. It has been found on sea-birds' nests on the guano islands off the coast of Peru. It is capable of transmitting relapsing fever under laboratory conditions.

ORNITHODORUS VENEZUELENSIS (Brumpt, 1921)

This tick is closely related to *O. talajé*, *O. capensis*, and *O. coniceps*.

Geographical distribution.—So far this species has been reported only from Venezuela and Colombia; it cannot live in the hot coastal plains where *O. talajé* abounds.

Characters.—The female is larger than the male, measuring 5-6 mm. by 3-4 mm. broad. Its home is in the mountains, at an elevation of 3,000-5,000 ft., where it lives in the walls of human habitations, often in company with bed-bugs. In habits it is very voracious; it bites savagely and repeatedly whilst expelling a liquid coxal fluid. Its development has been studied by Brumpt.

The engorged, fecundated female lays 50-100 eggs, in several batches. The hexapod larvæ, on emerging, are very active, engorge themselves in a few hours on mammalian blood, moult, and give rise to a nymph which feeds without undergoing an ecdysis, as in *talajé* and *coniceps*. These evolutionary characteristics are the main points which led to its recognition as a separate species. The nymph moults after each feed, and becomes adult after the fourth. This tick conveys relapsing fever, probably hereditarily, as in *O. moubata*, in Colombia and Venezuela.

ARGAS PERSICUS (Fischer, 1824); A. MINIATUS (Koch, 1844) (Plate XI, 4, facing p. 168)

This tick is found more commonly in the north and east of Persia, also in Syria, Turkestan, Russia, China, Algeria, and Cape Colony, in North and South America and the West Indies, West Australia and Queensland. It attacks both poultry and human beings, and infests old houses, living in the cracks of walls and floors.

Balfour has infected chickens with *T. gallinarum* by feeding them on the eggs of infected *Argas persicus*. This tick was formerly thought, on epidemiological grounds, to carry relapsing fever to man in Persia.

DERMACENTOR VENUSTUS (Banks, 1897); D. ANDERSONI (Stiles, 1908)

Geographical distribution.—This species is very abundant in the Rocky Mountains. The adult makes its appearance during the summer months, and is parasitic on horses, big game, and wild animals. It frequently feeds on man. (Figs. 309, 310.)

Characters.—The larvæ and nymphs are found on small rodents, especially ground-squirrels, which may act as the reservoirs of the virus of Rocky Mountain fever.

The developmental cycle is as follows: The female tick, when engorged with blood, some four to six days after quitting her host, deposits 5,000-7,000 eggs. The hexapod larvæ emerge on the sixteenth day, and very shortly, within two to eight days, proceed to engorge themselves with blood. After the larva has fallen to the ground and moulted, a nymph is produced which can survive in this state for 300 days, and this, too, after feeding, falls to the ground and moults.

The recently-developed male and female ticks are capable of fasting for two years. When they attach themselves to their mammalian host they gradually engorge themselves with blood, and copulate four days later. After a period of eight to fourteen days the gravid females fall to the ground and deposit their eggs, while the males remain still attached to their host. Under natural conditions, when interfered with by cold weather, the whole cycle may take two years.

THE LINGUATULIDÆ (PENTASTOMIDÆ)

The Linguatulids are degenerate arachnids having neither eyes nor feet. The body is annulated, giving them a rough resemblance to a tapeworm, but Van Beneden (1848) first recognized their arthropod nature. The mouth is surrounded by two pairs of primitive appendages. On the head are numerous symmetrically arranged papillæ, while the opening of some large epidermal glands is situated at the base of the mouth-parts. Respiration is carried out by cutaneous absorption. Part of the life-history is passed in an intermediary host. Two genera parasitic in man are at present recognized—*Linguatula* and *Porocephalus*.

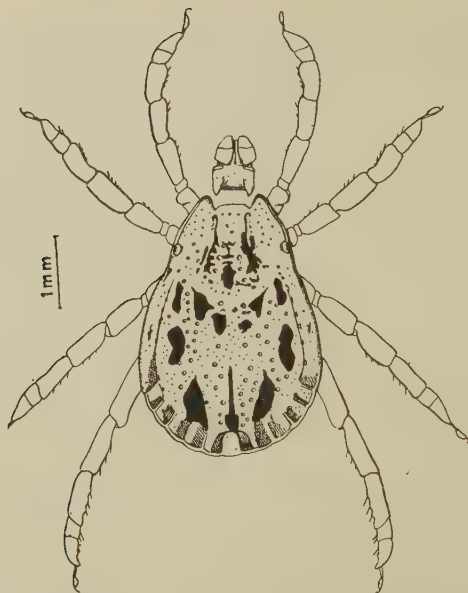


Fig. 309.—*Dermacentor venustus*, ♂. (By courtesy of Prof. Nuttall.)

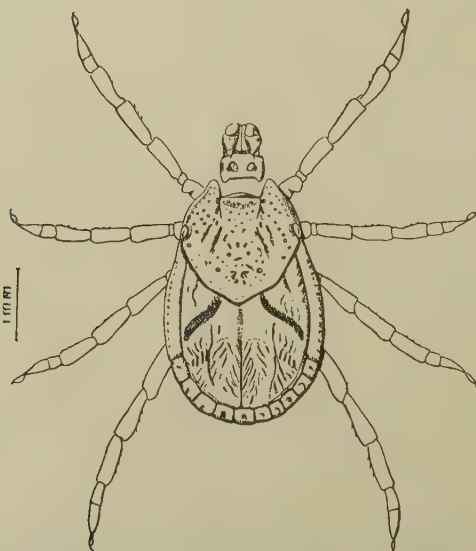


Fig. 310.—*Dermacentor venustus*, ♀. (By courtesy of Prof. Nuttall.)

LINGUATULA SERRATA (Frohlich, 1789)

Geographical distribution.—Southern Germany, Switzerland and Brazil.

Characters.—This linguatula (Fig. 311) is found in its adult state in the nasal cavity of dogs, wolves, and foxes; rarely in sheep or goats. The larvæ are met with frequently in the mesenteric glands of domestic animals, as well as in rabbits and hares, and have been found by Zenker in 4·6 per cent. of autopsies, in the liver of man, in whom they appear to cause no symptoms. In Brazil it has been recorded as an intestinal parasite. The infection seems to be acquired through eating raw vegetables contaminated by the nasal secretion of dogs.

The body of the parasite is somewhat pear-shaped and flattened, and transversely striated with about 90 rings; the mouth is roughly quadrangular in shape and surrounded by hooks. The intestine is simple. The male is white, 18–20 mm. long, and measures 3 mm. broad anteriorly, 0·5 mm. posteriorly. The female, 8–10 mm. in length, is grey, but may be brown when packed with eggs; anteriorly she measures 8–10 mm. broad, posteriorly 2 mm. The eggs are ovoid, and 90 μ in length by 70 μ in breadth.

Life-history.—The eggs contain ripe embryos when they are deposited by the female, and pass out with nasal mucus to become attached to grass and other herbs; they are then ingested by the definitive host, penetrate the intestinal coats, and enter the viscera, the liver, lung, mesenteric glands, kidney, etc. The larva, having grown to 5–6 mm. in length, encysts, and is ingested by various carnivora. It then migrates from the stomach, and grows into the adult form in the nasal fossæ of these animals.

POROCEPHALUS ARMILLATUS (Wyman, 1848)

Geographical distribution.—*P. armillatus* seems to be confined to tropical Africa, and hitherto, as regards man, to negroes only, among whom it is far from being uncommon. Salm has found a porocephalus encysted beneath the serous coat of the small intestine of a Djambi native in Java.

The adult form inhabits pythons and other snakes. It has been found in *Python sebae*, in the royal python (*P. regius*), and in the nose-horned viper (*Bitis nasicornis*). The larval—or, more correctly, the nymphal—form has been found in the lion, in the leopard, in the mandrill, in the aard-wolf, in the giraffe, in Syke's monkey (*Cercopithecus albicularis*), in the Pousargues guenon (*Cercopithecus pousarguei*), and in the African hedgehog (*Erinaceus æthiopicus*).

Characters (Fig. 312).—The body of the parasite is vermiform, yellowish, translucent, larger in females (9–12 cm. long by 5–9 mm. broad) than in males (3–4·5 cm. long by 3–5 mm. broad); cylindrical in the anterior half, slightly tapering posteriorly, and terminating in a blunt-pointed cone. It is characterized by the presence of prominent opaque rings 1–2 mm. wide, numbering 16 or 17 in the males, 18 to 22 in the females, placed somewhat obliquely and separated by interannular spaces 2–5 mm. wide, except between the first rings, which are faintly indicated by shallow linear furrows. There is no clear distinction between cephalothorax and abdomen, and the rings nearest the cephalothorax are sometimes so indistinct that it is almost impossible to make out their actual number. The cephalothorax is depressed, slightly convex on the dorsal, more or less concave on the ventral surface. It is rounded anteriorly; posteriorly it is limited by the first body-rings. It varies considerably in length; its breadth is from 4 to 7 mm.

The mouth, opening on its ventral surface about 1 mm. from the anterior border, is lipped by a chitinous ring. Above it are two prominent papillæ. On either side of the mouth are two protractile chitinous hooks similar in shape to feline claws. The anus is terminal at the posterior end. The genital orifice of the male is at the anterior end of the abdomen, in the middle of the ventral surface of the first body-ring; that of the female opens in the middle of the ventral surface of the caudal cone at about 1 mm. from the anus. The female is oviparous; the eggs are broadly elliptical, double-shelled, and measure $108\ \mu$ in length by $80\ \mu$.

The nymphal form is usually found spirally coiled within a cyst, the ventral surface corresponding, as a rule, to the convexity of the curve. In shape and structure the nymph closely resembles the adult, and the

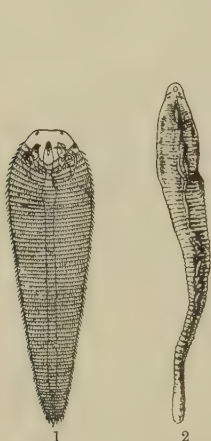


Fig. 311.—*Linguatula serrata*. (After Brumpt.)

1, Larval form ($\times 6$);
2, mature form (nat. size).



Fig. 312.—*Porocephalus armillatus*. Nat. size.
(After Sambon.)

number of rings is the same. Calcification of the nymphal form in the liver may take place.

Life-history.—Little until lately was known of the life-history of *P. armillatus*, but apparently it is similar to that of the European linguatulid (*Linguatula serrata*). The eggs, disseminated by snakes harbouring the adult form, reach the intermediary host probably with food or drinking-water. That this is the probable route in man is shown by the work of Broden and Rodhain, who gave porocephalus eggs to sleeping-sickness patients, and afterwards found the nymphal forms in their livers at autopsy. After entering the stomach the larvæ penetrate the mucosa, where some remain (Fülleborn); others pass on and become encysted in almost any organ or tissue, more especially liver, mesentery, or lungs. At a certain stage of development they escape from their cysts and migrate to the serous cavities, where they cause considerable inflammation. As a rule, at this stage they are swallowed by their definitive host.

Noc and Curasson state that in *Cercopithecus* the nymphal forms take 86

days to develop, while in the definitive host (*Python sebae*) a further 106 days are required for the parasites to reach maturity.

Pathogenesis.—There is much uncertainty as to the pathogeny of this parasite. Some consider it quite harmless. There can be no doubt as to the gravity of a heavy infection at the time when the parasites are migrating in their intermediary host. In Kearney's case, reported by Aitken, twenty or thirty parasites were found encysted in the liver and one or two in the lungs. The lungs were greatly congested. In Marchoux and Clouard's case the parasites were found in the liver and in the mesentery all along the intestine, but especially about the cæcum. In Chalmers's case numerous parasites were found moving freely in the abdominal cavity over the surface of the various organs. A large number were found within the lumen of the small intestine. Many were still encysted in the lungs.

That this worm is pathogenic to monkeys when present in large numbers was shown by Fülleborn's experiment, in which one monkey died after 60 days, the other 300 days after being fed upon the tracheal mucus of infected snakes.

The diagnosis of porocephalus infection during life is impossible.

INSECTA

The Insecta are easily distinguished from the other arthropods by the division of their body into head, thorax, and abdomen, by the presence of three pairs of legs situated on the thorax, and of one pair of antennæ on the head.

The method of *reproduction* is important. The sexes are separate, the male being distinguished from the female by its smaller size, or in certain cases by the character of its antennæ, and very often by its different mode of life. The male may be parasitic on plants, while the female feeds on animal blood or tissues. *Parthenogenesis*, or reproduction by unfertilized eggs, is common. Certain species are viviparous. The egg, which in some cases is laid in water, as a rule contains much food material. The young may be aquatic organisms; they differ markedly in appearance and mode of life from the adults, and are then known as larvæ. The full-grown larva undergoes a resting stage known as the pupa, from which the adult organism, or imago, emerges. An insect which passes through all stages in the course of its development is said to show *complete metamorphosis* (Fig. 313); while others, in which the young when born resemble their parents to a certain extent, and become adult by a series of moults, are said to show *incomplete metamorphosis*.

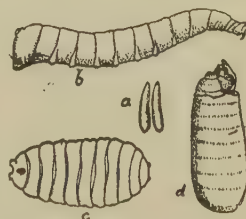


Fig. 313.—Life-history of *Musca domestica*.

a, Eggs; b, larva; c, pupa;
d, empty puparium.

ORDER DIPTERA

Flies possess only an anterior pair of membranous wings, the posterior pair being represented by halteres. The mouth-parts are adapted for sucking or piercing. The number of visible abdominal segments is 4-9.

The nematoceros Diptera include many groups of medical interest—for instance, *Culicidæ*, or mosquitoes; *Psychodidæ*, or sandflies; *Chironomidæ*, or midges; *Simuliidæ*, or buffalo-gnats.

The brachyceros Diptera are represented by the *Tabanidæ*, or gadflies.

The MUSCIDÆ include *Musca*, the housefly; *Calliphora*, the bluebottle; *Auchmeromyia*, the Congo floor-maggot; and *Cordylobia*, the "Tumbu fly"—the latter two being partially parasitic on man in their larval stages. The blood-sucking muscids are represented by *Glossina*, the tsetse-fly, and *Stomoxys*, the stable-fly.

The SARCOPHAGIDÆ, or flesh-flies, are viviparous, and deposit their larvæ in wounds and in the nasal passages.

The larvæ of CESTRIDÆ, or bot-flies, may be parasitic in the subcutaneous tissues, as *Dermatobia*, the "Macaw-worm."

Among the pupiparous Diptera—flies which give birth to a full-grown larva, one at a birth—may be cited *Hippobosca*, which is normally parasitic on mammals and birds.

For further information the student is referred to a textbook such as Alcock's "Entomology for Medical Officers."

Family Culicidæ

The geographical range of the mosquito extends from the Arctic zone to the equator and to both hemispheres. Given stagnant or slow-flowing water and a summer temperature, this family of insects will be represented by one or many species. The distribution of particular species and the abundance of mosquitoes in any given place are determined, in addition to temperature and hydro-meteorological conditions, by various complicated circumstances.

The adult insect feeds on vegetable juices; the males, with few exceptions, exclusively so. In addition to a vegetable diet, the females of most species, when opportunity offers, suck the blood of mammals and birds. The male mosquito, not being a blood-sucker, takes no part in the diffusion of disease; it is the female only that is a germ-carrier. (Fig. 314.)

Soon after impregnation the female lays her eggs (Figs. 315, 316, 317) from time to time—singly, in groups, or in boat-shaped masses, according to species—either on the surface of still water, on which they float, or in proximity to water. The process of hatching out depends in great measure, as indeed do all the developmental processes connected with the mosquito, on temperature, being retarded or even suspended by cold and accelerated by warmth. In some species the eggs remain dormant throughout the winter or through a long spell of dry weather, but in ordinary circumstances the larvæ hatch out in from two to three days, and at once proceed to feed voraciously on the organic material suspended in the water. Being air-breathers, a great part of their time is passed at the surface of the water, where they lie in such a position—which varies with species—that the respiratory opening, placed near the tail, can function readily (Figs. 318, 319). After several moults the larva, now very much increased in size, passes to the nymph or pupa phase (Figs. 320, 321), during which it ceases to feed, and for the most part floats just awash at the surface of the water. In from one to two days the pupa-case bursts and the insect, emerging, stands on the empty case till its wings have dried, when it flies away. From first to last, from egg to imago, the process of development takes about a month in the temperature of the Italian summer; but a much shorter time (seven to ten days) may suffice in a tropical climate. As each female mosquito may lay eggs many times in a season, and many hundreds of eggs each time, and as the young female can produce eggs within a week or ten days after

her emergence from the pupa-case, it follows that one pair of insects can give rise to a large progeny in the course of a summer.

During cold weather the development of the larva is temporarily suspended, and the surviving adults, at all events the females, hibernate in

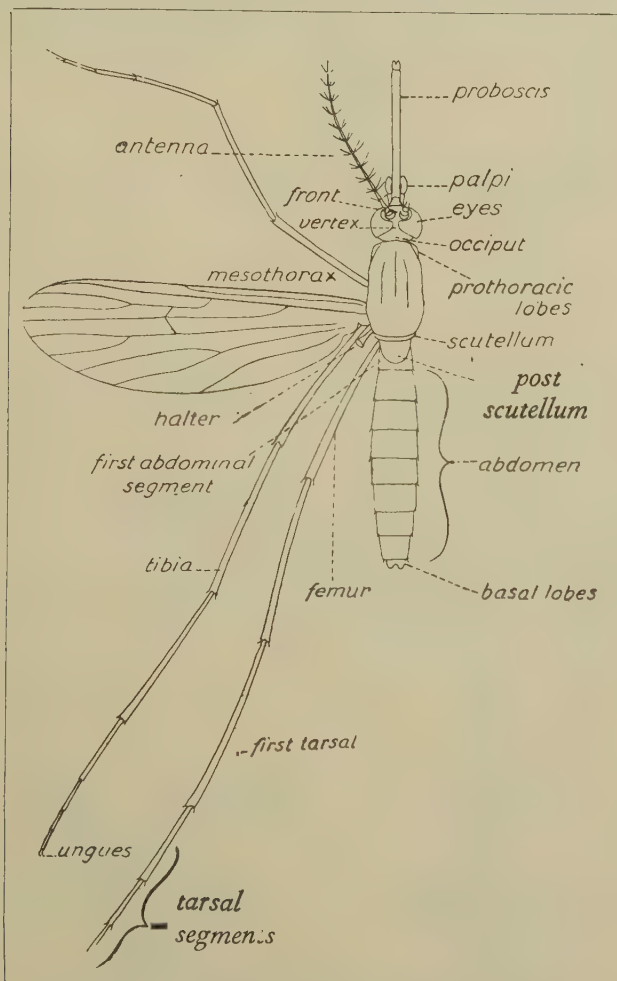


Fig. 314.—Female mosquito, to show anatomy.

dark and sheltered places, to become active again on the return of warm weather. In this way the species is carried over the cold weather of winter, though there are some that hibernate in the larval stage and others in the egg. The duration of the life of the adult insect has not been definitely

ascertained; it is known that some species, if supplied with water and suitable food, can live for several months.

It is suggested that the mosquito tends to return to the particular pool in which she herself was hatched out, to deposit her own eggs, and that she rarely strays from the vicinity more than a few yards, quite exceptionally beyond half-a-mile. Occasionally she may be blown for some distance by gentle winds; and it is believed that in certain circumstances, probably

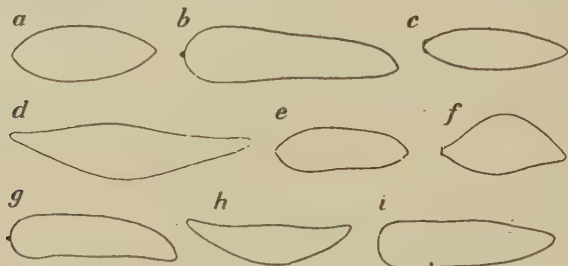


Fig. 315.—Various forms of mosquito eggs.

a, *Grabbamia dorsalis*; b, *Culex pipiens*; c, *Culex scapularis*; d, *Mansonia titillans*; e, *Aedes argenteus*; f, *Tæniorhynchus fulvus*; g, *Culex fatigans*; h, *Tanithinosoma lutzi*; i, *Tæniorhynchus fasciolatus*.

connected with food supply and overstocking, she will travel singly or in vast swarms for long distances. Such migrations, however, are quite unusual. Of course, mosquitoes may be, and often are, transported great distances in ships, railway carriages, and similar vehicles, and in this way man aids in their diffusion; but for the most part the mosquito is a feeble and timid flyer, disliking to leave her accustomed haunt, and seldom rising high above the ground. So soon as even a moderate breeze springs up, she seeks shelter in bush, or house, or cranny. Some species are domestic;



Fig. 316.—Eggs of *Anopheles maculipennis*.

a, Under side; b, upper side.

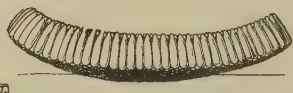


Fig. 317.—*Culex fatigans*: eggboat. (After Sambon.)

others live exclusively in jungle or forest; some, after passing the day in the open, visit human habitations or the haunts of birds and beasts during the night. The great majority of species are nocturnal in habit, although many of these can be coaxed into activity by the reproduction of night-like conditions of shade and atmospheric stillness.

Fig. 314 gives a good idea of the leading features of the anatomy of the mosquito and of the names applied to the various parts and organs,

and will help the student to understand descriptions of genera and species. For distinctions based on scale characters, see Figs. 327-9.

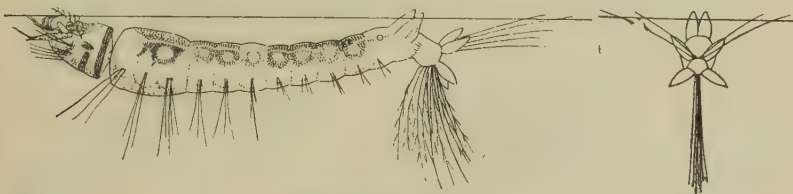


Fig. 318.—Larva of *Anopheles maculipennis* Meigen, showing breathing position at surface of water. (After Howard, "Bull. United States Dept. Agr.")

The antennæ of the male insect (Figs. 322, *a*, and 323, *a*) are usually adorned with a profusion of long, silky hairs, in marked contrast to the scanty, down-

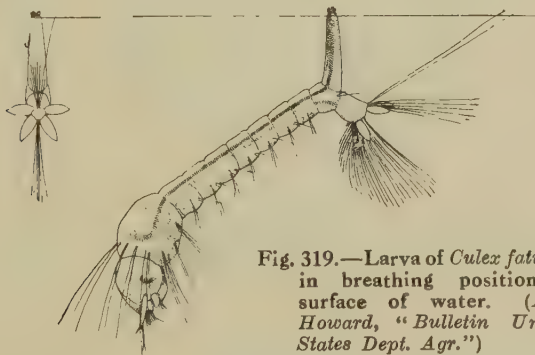


Fig. 319.—Larva of *Culex fatigans* in breathing position at surface of water. (After Howard, "Bulletin United States Dept. Agr.")

like, and short hairs on the antennæ of the female; this is an easily recognized indication of sex in most species.



Fig. 320.—Pupa of *Anopheles maculipennis*.



Fig. 321.—Pupa of *Culex fatigans*.

The proboscis consists of a number of piercing elements enclosed in a sheath—the labium, which, at its free end, is tipped with two minute labella. In feeding, the mosquito raises her hind-legs and presses the tip of the proboscis against the skin. This causes the labella (Fig. 324, *h*) to splay

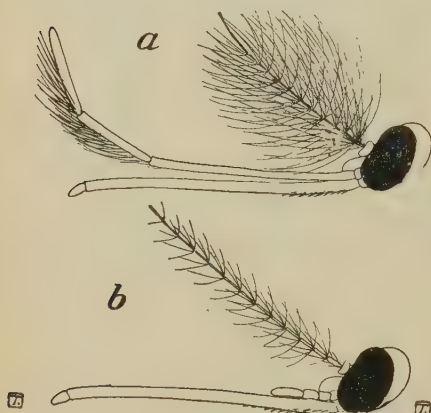


Fig. 322.—Heads of Culicini.

a, Male; *b* female.

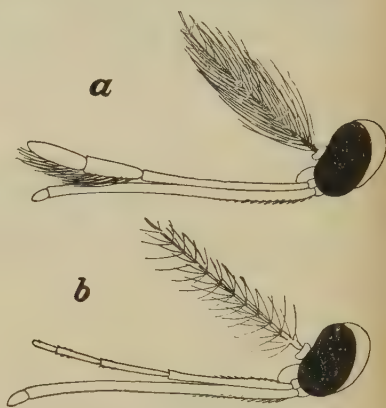


Fig. 323.—Heads of Anophelini.

a, Male; *b*, female.

out and so serve as a support to the piercing elements—namely, the labrum, hypopharynx, mandibles, and maxillæ (Figs. 324, 325)—which are now thrust into the skin. The labium does not penetrate; as the stabbing elements

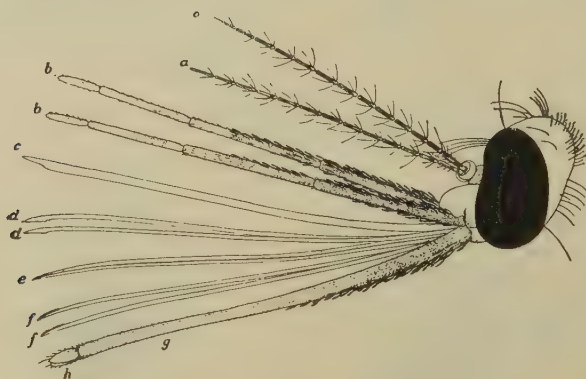


Fig. 324.—Mouth-parts of female mosquito.

a, *a*, Antennæ; *b*, *b*, palpi; *c*, labrum-epipharynx; *d*, *d*, mandibles; *e*, hypopharynx; *f*, *f*, maxillæ; *g*, labium; *h*, labella.

sink into the skin the proboscis sheath bends backwards about its middle, the labella still pressing against the skin and clasping the stylets. The secretion of the salivary glands passes along the salivary duct, and thence down a minute canal which traverses the hypopharynx to its tip,

and so into the subcutaneous tissues of the bitten animal. It is supposed that the function of this secretion is, by irritating, to determine a flow of blood to the part bitten, and also prevent coagulation of the blood. To many people this secretion is a powerful irritant, although repeated inoculation tends to produce tolerance, as in the case of many other organic poisons.

A buccal tube is formed by the apposition of the upper surface of the hypopharynx to the under-surface of the labrum (Fig. 325). Along the tube so formed the blood is aspirated by the expansion of the gizzard-like organ, and then driven by the contraction of the same into the stomach, or middle intestine as it is called. A mosquito will fill herself in a



Fig. 325.—Section of mosquito's proboscis.

(Adapted from Nuttall and Shipley.)

c, Labrum-epipharynx; d, mandible; e, hypopharynx; f, maxillæ; g, labium
i, salivary duct; j, muscles; k, trachea.

minute or thereabouts. She then withdraws her proboscis and flies heavily away to some sheltered spot to digest the meal. Apparently the first step in digestion is the concentration of the blood she has imbibed; this is effected by excretion of the watery portion of the liquor sanguinis. Often while this process of dehydration is proceeding, even while she is sucking, droplets of clear fluid may be seen ejected at her anus. The concentrated blood becomes in this way a viscid tarry mass, which is gradually, in the course of three or four days, partly absorbed, and partly voided as gamboge-coloured fæces. The mosquito is now ready for another meal.

The rich pabulum supplied by blood seems to favour ovulation.

Many kinds of insect possess blood-sucking propensities. As a rule there is little difficulty in distinguishing most of these from the mosquito. There are certain diptera, however, which closely resemble the latter in their appearance as well as in their habit. These the student should learn to distinguish.

The principal of the mosquito-like blood-suckers are the Midges (*Chironomidæ*) and the Sandflies (*Phlebotomus*). The following are the diagnostic points:

Mosquitoes have a long suctorial proboscis, and the veins of their wings are fringed with scales. (Fig. 326.)

Midges (*Chironomidæ*) are very slender and minute, have a short suctorial apparatus, and their wings are devoid of scales.

Sandflies (*Phlebotomus*) are small, slender, and very shaggy; have a

comparatively short suctorial apparatus, comparatively long legs, narrow, pointed, hairy wings, and long, hairy antennæ.

Most authorities separate the Culicidæ into two subfamilies, namely —(1) Corethrinæ, in which the proboscis is short and not formed for piercing; (2) Culicinæ, or typical mosquitoes with elongate proboscis. The Culicinæ, again, are arranged in four natural tribes.

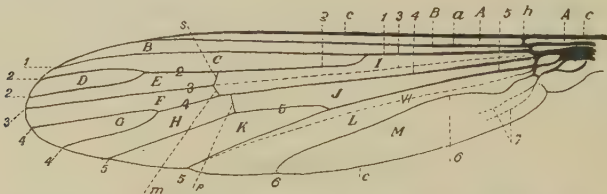


Fig. 326.—Wing of *Culex* (male), to illustrate terminology.

c, Costa; a, auxiliary vein; 1-6, first to sixth longitudinal veins and branches; 7, seventh or false (unscaled) longitudinal vein; VI, unscaled vein between fifth and sixth longitudinal veins; h, humeral transverse vein; s, supernumerary transverse vein; m, middle transverse vein; p, posterior transverse vein; A, costal cells; B, subcostal cells; C, marginal cell; D, anterior fork cell or first submarginal cell; E, second submarginal cell; F, first posterior cell; G, hinder fork or second posterior cell; I, first basal cell; J, second basal cell; K, anal cell; L, axillary cell; M, spurious cell.

GENUS ANOPHELES Meigen (Plate I, facing p. 8)

Head only moderately broad, usually covered with upstanding forked scales, though scales of other kinds are also present in a few species (Figs. 327-9). Maxillary palps long and spatulate in the male; as long as, or not much shorter than, the proboscis in the female. Free edge of scutellum simply convex, not trilobate; post-scutellum bare. Abdomen either sparsely hairy or with localized patches of scales; sometimes with a considerable expanse of scales, which, however, never form a uniform, complete, and compact invest-



Fig. 327.—Graphic key to distinctions based on scale characters.

a, b, c, Narrow curved scales; d, e, f, hair-like curved scales; g, h, upright forked scales; i, j, long twisted scales; k, large lanceolate scale; l, m, small narrow lanceolate scales; n, large expanded scale; o, p, spindle-shaped scales; q, broad flat scale; r, s, broad irregular scales.

ment. Wings commonly dappled or profusely speckled, but occasionally quite spotless. Legs remarkably elongate. (Figs. 330, 331.) In repose

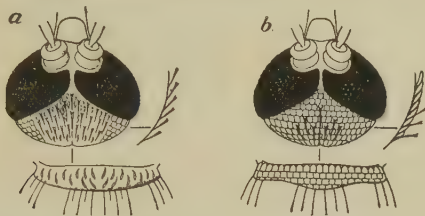


Fig. 328.—Various types of "scale vestiture."

(Such scale characters are now regarded as specific and not of generic importance.)

a, *Anopheles*, head, scutellum, and lateral view of head scales; b, *Aedes (Stegomyia) argenteus*, head, scutellum, and lateral view of head scales.

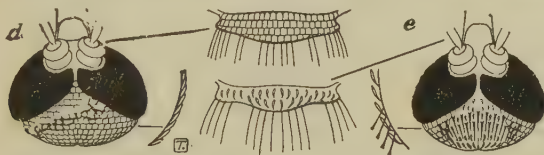


Fig. 329.—Continuation of Fig. 328.

d, *Megarhinus*, head, scutellum, and lateral view of head scales; e, *Culex*, head, scutellum, and lateral view of head scales.

the body is usually inclined at an angle with the resting surface. (See Figs. 333, 334.)

The eggs are boat-shaped, and with rare exceptions have their investing membrane inflated laterally to form a pair of floats.



Fig. 330.—*Anopheles maculipennis*, female.



Fig. 331.—*Anopheles funestus*, female.

The larva has the head at least as long as broad, and has four bristles or feathered hairs projecting from the free edge of the clypeus. The long lateral hairs of the thorax and abdomen are strongly feathered. Some or all of the abdominal segments as far as the seventh carry dorso-laterally a pair of characteristic rosettes or cockades of scales. The breathing openings are situated in a hollow on the dorsum of the eighth segment, the hollow being bounded laterally and posteriorly by a system of folds or valves, whereby the larva assumes a horizontal position (Fig. 318).

The larvæ occur not only in all kinds of stagnant water, but also in pools in the beds of rivers and mountain streams, or even in the current if there are also floating weed and debris for their protection, in domestic



Fig. 332. — Resting position of *Culex fatigans*.



Fig. 333. — Resting position of *Anopheles hyrcanus*.



Fig. 334. — Resting position of *Anopheles maculipennis*.

water-vessels, and occasionally in the water that collects in holes in trees; some species thrive in brackish or salt water, and each species has its own particular kind of habitat.

As regards the capabilities of any particular species of anopheline as a factor in the transmission of malaria, it is necessary that one should ascertain, as Swellengrebel, Schüffner and de Graaf have pointed out, whether the species occurs in numbers; whether the parasites of malaria can complete their development in its body; whether it habitually feeds in nature on human blood; whether it feeds in the jungle or visits man in or near his dwelling places; what is the vegetable food of the female and whether this substance interferes with the development of the malaria parasites. One of the points recently brought out is that a species proved to be a natural carrier of malaria in one situation sometimes does not appear to play an important part in another. Thus *A. aconitus* has proved to be a good carrier of malaria experimentally, and has been found naturally infected in Malaya and western Java, yet in another part of the East Indies over 1,000 specimens have been dissected with negative results. Again, in North America *A. crucians* is found to be an effective carrier only when bred in brackish water. Again, *A. rossii* plays little or no part in the transmission of malaria, but yet on occasions during the height of an epidemic it has been found to be infected in Java to the extent of 8.6 per cent. But even there this species plays a minor part.

SPECIES KNOWN TO CARRY THE MALARIA PARASITE

EUROPE.

- A. bifurcatus*. B.T. and M.T.
- A. hyrcanus*. B.T., M.T. and Q.
- A. hyrcanus* var. *pseudopictus*. B.T., M.T. and Q.
- A. maculipennis*. B.T., M.T. and Q.
- A. plumbeus*. B.T. and M.T.

ASIA.

- A. aconitus*. M.T.
- A. barbirostris*. B.T. and M.T.
- A. bifurcatus*. B.T. and M.T.
- A. culicifacies*. B.T., M.T. and Q.
- A. elutus*. (Palestine.) B.T. and M.T.
- A. fuliginosus*. B.T., M.T. and Q.
- A. hyrcanus* var. *sinensis*. (China.) B.T.
- A. hyrcanus* var. *nigerrimus*. (India and Malaya.) B.T., M.T. and Q.
- A. hyrcanus* var. *peditonatus*. (Malaya.) B.T., M.T. and Q.
- A. hyrcanus* var. *argyropus*. (Dutch E. Indies.) B.T., M.T. and Q.
- A. kochi*. B.T. and M.T.
- A. leucosphyrus*. B.T., M.T. and Q.
- A. listonii*. B.T., M.T. and Q.
- A. ludlowii*. B.T., M.T. and Q.
- A. maculatus*. M.T.
- A. maculipalpis*. M.T.
- A. maculipennis*. B.T., M.T. and Q.
- A. minimus*. M.T.
- A. multicolor*. M.T.
- A. punctulatus* var. *moluccensis*. B.T. and M.T.
- A. stephensi*. B.T., M.T. and Q.
- A. superpictus*. B.T. and M.T.
- A. tessellatus*. M.T.
- A. umbrosus*. B.T. and M.T.
- A. vagus*. B.T. and M.T.
- A. willmori*. B.T.

AFRICA.

- A. bifurcatus*. B.T. and M.T.
- A. funestus*. M.T. and Q.
- A. gambiae* (formerly *costalis*). Q.
- A. multicolor*. M.T.

NORTH AMERICA.

- A. crucians*. B.T. and M.T.
- A. punctipennis*. B.T. and M.T.
- A. quadrimaculatus*. B.T., M.T.

SOUTH AMERICA.

- A. albimanus*. B.T. and M.T.
- A. albitarsis*. B.T. and M.T.
- A. argyritarsis*. B.T. and M.T.
- A. crucians*. B.T. and M.T.
- A. pseudopunctipennis*. M.T.
- A. punctipennis*. B.T. and M.T.
- A. tarsimaculatus*. M.T.

SPECIES KNOWN TO CARRY THE MALARIA PARASITE (*continued*).

AUSTRALIA.

A. annulipes. (?)*A. punctulatus*. M.T.*A. punctulatus* var. *moluccensis*. B.T. and M.T.

Note: This list has been compiled from the complete summary by Maj. G. Covell, I.M.S. (Ind. Med. Res. Memoirs, No. 7., 1927.)

GENUS CULEX (Linn., 1758)

This genus contains a large number of species, of which two are of historical and medical interest. Eggs and larvæ are illustrated in Figs. 317, 319.

CULEX FATIGANS (Wiedemann, 1828) (Figs. 332, 335)

Synonyms.—*C. skusei* Giles 1890; *C. quinquefasciatus* Say, 1823.

This is a nocturnal species—often incorrectly mistaken for *C. pipiens*, but it is a denizen of the tropics and subtropics, and is commonly found in human habitations; it is, in fact, a domestic species. It breeds in water-tubs or in any collection of stagnant water.

Its chief claim to interest is the fact that this species was first discovered by Manson in 1879 to be the intermediary host of *Filaria bancrofti*, and was suspected to be the transmitter of the virus of dengue by Graham in 1903.

The mosquito also acts as intermediary for the filaria of the dog, *Dirofilaria immitis*, and the *Proteosoma* of birds. A description of eggs and larvæ is given at p. 804.

CULEX PAPIENS (Linn., 1758)

This mosquito is widely distributed in temperate regions. It is a domestic and nocturnal species, breeding in any collection of stagnant or semi-stagnant water.

It is now known to transmit *F. bancrofti* in China. *C. pipiens* differs mainly from *fatigans* in the characters of the male genitalia, but in its habits it is very similar.

GENUS AÆDES (Meigen, 1818)

The members of this genus of tropical interest are those mosquitoes which were formerly described as *Stegomyia* by Theobald, and are still generally known under that name. They are mostly black-and-white insects with white, silvery, or yellow lines, bands, or spots on the thorax and legs. In India they are known as "tiger mosquitoes," on account of their striped appearance. They seem to have a decided preference for the littoral, and certain species (*A. argenteus*, *A. albopictus*) are frequently found on ships, and are no doubt distributed by this means. At present the subgenus *Aëdes* (*Stegomyia*) includes many species which are identifiable by their striking thoracic and other ornamentation.

The distinctive characters are: In the female the palpi are short; in the male they are usually longer than the proboscis, the last two joints being up-turned and sparsely haired. The vertex is covered with broad, flat scales with a few or no narrow scales on the nape. The thorax is usually conspicuously ornamented, while the eighth abdominal segment in the female is large and retractile.

The eggs, instead of being cemented in rafts, are deposited separately, each being surrounded by small air-chambers. They are capable of withstanding a considerable degree of desiccation. The *larvæ* maintain an almost vertical attitude in water. They have short, smooth antennæ, with not more than three hairs in a shaft tuft. The frontal hairs are single; the siphon is short, not much more than twice as long as broad. The hair-tuft is situated about the middle of it, and the comb teeth occur in a single row.



Fig. 335.—*Culex fatigans*, male and female.

(After A. Eysell, Mense's "Handbuch der Tropenkrankheiten," 3rd edit.).

ÆDES ARGENTEUS

Synonyms.—*Stegomyia fasciata* (Fabr., 1805); *Culex ægypti* (Linn., 1762).

A. argenteus (Plate XII, facing p. 190) can be recognized by the peculiar lyre-shaped ornamentation of its thorax—two dull-yellow parallel lines in the middle and a curved silvery line on each side. The proboscis is not banded; the abdomen is banded basally; the last hind tarsal joint is all white, and some of the other tarsal joints are marked by light bands basally. This widely distributed species is essentially a domestic form; it bites with avidity. It breeds in small artificial collections of water, such as barrels, puddles, cisterns, sagged rain-gutters, and even in such small receptacles as sardine-tins; the nature of the water appears to be a matter of indifference. The eggs resist a considerable degree of desiccation, and, as they may sink to the bottom of the water in which they lie, they are readily pumped into water-tanks of ships, and may even be dried and remain viable when placed in an envelope and sent through the post from far-off Africa and Central America. This species transmits the virus of yellow fever and that of dengue (Bradley and Macdonald).

Although widely distributed, *A. argenteus* does not occur abundantly in certain parts, such as Australia, the Malay States, China, Africa, and the West Indies, where its place is taken by other species which greatly resemble it.

ÆDES (STEGOMYIA) ALBOPICTUS (Skuse, 1895)

Synonym.—*Stegomyia scutellaris*.

A very common and widely distributed species in the East, where it breeds in artificial receptacles in the vicinity of dwellings, as well as in tree-holes bamboos, etc. Is said to be the transmitter of dengue



Fig. 336.—Diagrammatic representations of marking on thorax of (A) *Aedes albopictus* and (B) *Aedes variegatus*—lateral views.

fever in Japan (Yagamuchi, Koizumi, and Tonomura). The development of *F. bancrofti* in this mosquito is arrested about the seventh day. In general habits it resembles *A. argenteus*. It is easily distinguishable from that species by the single broad median stripe which adorns the scutum. (Fig. 336, A.)

ÆDES (STEGOMYIA) VARIEGATUS (Doleschal, 1858). (Plate XXXI, facing p. 542.)

Synonym.—*Stegomyia pseudoscutellaris*, Theobald.

This species is widely distributed in the Pacific islands, where it replaces *A. albopictus*. It occurs also on Christmas Island and in New Guinea, and acts as the chief transmitter of the non-periodic filaria (*F. bancrofti*) of those regions. It is diurnal in habit, and may be distinguished by three parallel white stripes on the mesothorax and incomplete white abdominal cross-bands (Fig. 336, B). The larva resembles that of *A. argenteus* (Fig. 337), from which it can be distinguished by lateral barbs of the combscales which are distinctly smaller and more delicate than those of *A. argenteus*. The breeding-places of this insect are peculiar. It is not in any way a domestic species like the preceding; its main requirements are small collections of fresh water containing decayed vegetable matter, in husks and shells of coconuts; in crevices and holes in trees; in the artificial reservoirs hewn out of coconut trees and used as wells by the Pacific islanders; in holes in coca-pods gnawed out by the Pacific rat; in bottles and tins which may be lying about in sheltered spots in the bush.

Both larvæ and pupæ can exist for a long time at the bottom of these breeding-places after the water has evaporated.

This species is extremely intolerant of sun and wind ; its main haunt is the still, shady, thick bush round native villages.

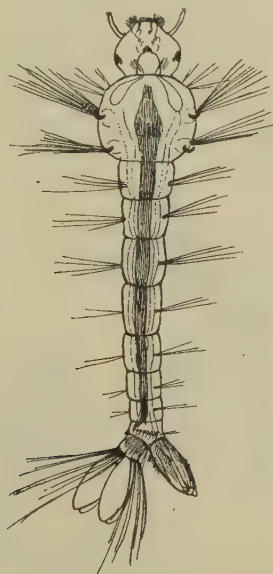


Fig. 337.—Larva of *Aedes argenteus*. (Orig.)

Family Psychodidæ

GENUS PHLEBOTOMUS (SANDFLIES)

These are minute and very hairy flies, from 1.5 to 2.5 mm. in length, and are easily recognizable. Only the females suck blood, and in some people their bite causes a considerable local disturbance ; in others, little or none.

These insects carry several diseases, notably phlebotomus fever (p. 210) ; there is also good reason for suspecting that they act as the carriers of leishmania of oriental sore and kala-azar (pp. 151, 132). *P. verrucarum* is believed by Townsend to transmit the virus of Oroya fever (p. 233) in the Andes.

The geographical distribution of the sandflies in the tropics and subtropics is a wide one. *P. papatasi* has been taken as far north as Paris (Langeron), and occurs throughout Southern Europe, especially in Italy and Dalmatia, in the Mediterranean basin, in North and East Africa, as well as in Java and India.

The greater part of the body is covered with long, yellow "hairs," among which there may be patches of scales. The antennæ have 16 joints. The proboscis is comparatively short ; it is as long as the head, and contains a number of piercing organs.

The wings are definitely pointed ; on removal of the outer "hairs" the venation can be distinctly seen. The legs are long and slender, and the abdomen is divided into 10 segments.

In the *female* the abdomen is spindle-shaped, and is provided with an upper and a lower pair of small claspers. In the *male* there are four pairs of sexual appendages—the upper and lower claspers and various other structures known as “submedian lamellæ,” “intermediate appendages,” and “the intromittent organ” (Newstead). (Fig. 338.)

While feeding, *Phlebotomus* is easily disturbed, the slightest movement of the skin being sufficient to put it to flight. It thrusts the somewhat stout rostrum downwards, while the maxillary palpi diverge a little. Blood can be seen entering the stomach within 60 seconds of haustellation.

Life-history.—Considerable moisture is apparently necessary to induce oviposition. The eggs, which are laid singly, are 0·385 mm. in length by



Fig. 338.—*Phlebotomus papatasi*. $\times 10$.
(After Whittingham, “Brit. Med. Journ.”)

- 1, Fully developed male imago. a, Hairy wings; b, antennæ; c, labial palps; d, eye; e, halteres; f, claspers; g, genital spines.
- 2, Fully developed female imago. Body hairs arranged in tufts; abdomen (a) spindle-shaped; b, ovipositors; c, proboscis.

0·12 mm. in breadth, and are thinly covered with a viscous substance. (Fig. 339.) A few hours after being laid they become darker in colour. Six to nine days after deposition they hatch into 12-segmented caterpillar-like larvæ, characterized by two very long dorsal bristles on the terminal segment. Each segment bears a number of spines arranged in a transverse row. The head is armed with formidable large and dentate mandibles, which are at first white, but afterwards become dark brown. (Fig. 339, 2). The newly hatched larva is sluggish, lies flat, with caudal bristles extended in the same plane, and progresses by slow undulating movements. It commences to feed on decaying nitrogenous material—it may be the bodies of defunct parent flies or the dejecta of lizards. The duration of the larval stage varies con-

siderably, but in favourable circumstances the larval life of *P. papatasi* is about four weeks. According to Whittingham, there are four distinct stages in the larval life, with a complete moult between each. The first instar lasts on an average seven days, and is characterized by an egg-tooth on the dorsum of the head; the second instar occupies about five days, the third the same period, during which the terminal segment becomes pigmented (Fig. 339, 3); the fourth, about nine days in Malta, where the whole life-cycle takes seven to eight weeks in July and August, with a mean daily humidity of 50-60 per cent. (Fig. 339, 4.)

The pupa is ochreous-buff in colour, and bears the thoracic appendages free from the body; the integument is covered with minute squames, and

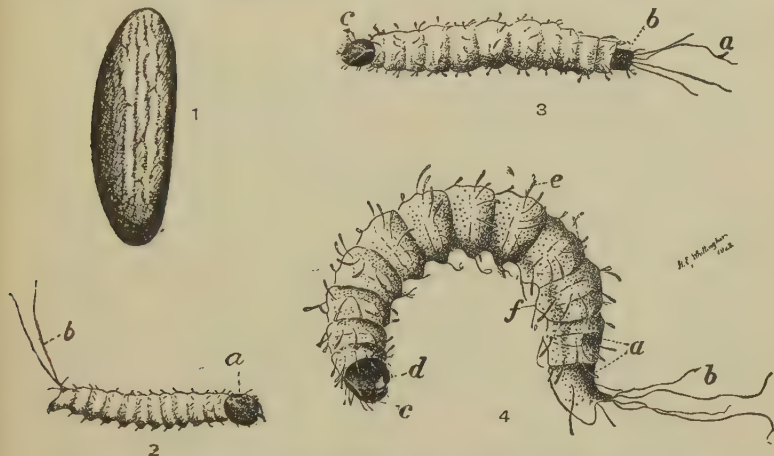


Fig. 339.—To illustrate life-history of *Phlebotomus papatasi*.
(After Whittingham, "Brit. Med. Journ.")

- 1, Fertilized egg, seven days after oviposition. $\times 80$.
- 2, First stage of larval life, two days old. *a*, Head with Y-shaped mark and egg-tooth; *b*, caudal bristles. $\times 40$.
- 3, Third stage of larval life (dorsal view), thirteen days old. *a*, Caudal bristles; *b*, last segment; *c*, antennae. $\times 20$.
- 4, Fourth stage, twenty-two days old. *a*, Last segment; *b*, caudal bristles; *c*, mandibles; *d*, labial plate; *e*, body hairs; *f*, false legs. $\times 20$.

small spines are present on the sides of the thorax and abdomen. In Malta the duration of the pupal stage is about nine days. The imago hatches out between midnight and 4 a.m., when the atmospheric humidity is high. The eggs are laid in dark, damp places where organic matter is present as food for the larvæ; usually this occurs in cracks or in masonry and at the base of walls and in stables, etc. Whittingham has shown that a very considerable amount of moisture is necessary for the successful rearing of these insects. In the situations indicated, moisture is possibly obtained from the water of condensation that collects there at night-time. Under artificial conditions Whittingham has succeeded in rearing the insects in cages containing sterilized nitrogenous matter at 80° F.

The adults are crepuscular and nocturnal in habit and are most active on warm, still nights. Sunlight repels them, but artificial light, especially

if not too bright, appears to attract them. Their flight is feeble and short, and when enclosed in a mosquito-net or on the bedclothes they appear to hop or glide for short distances.

For the classification of these insects, entomologists have relied upon slender differences afforded by the venation of the wings, the segmentation of the palpi, and the number and arrangement of the bristles or spines on the claspers. Larrousse recognizes 6 species in Europe, 11 in Asia, 4 in Java and the Philippines, 11 in Africa, and the same number in America.

The best-known species are *P. papatasi*, *P. perniciosus*, and *P. minutus* in Europe; *P. argentipes*, *P. perturbans* from India; *P. major* and *P. sergenti* from China; and *P. duboscqui* from Central Africa.

The bionomics of *Phlebotomus argentipes*.—Probably the vector of kala-azar in India, this insect has been extensively studied during recent years.

The insects are caught in cattle-sheds, human sleeping-quarters and chicken-houses. The adult females are pure blood-feeders on man or the domestic cow; in the intestines of the male, nothing has been found but the remains of the larval feed. The flight of the female is very limited.

In the laboratory the whole cycle of development occupies about thirty days; the eggs hatch in six days, the larval stage occupies fourteen, and the pupal stage, seven. The female feeds on the second day after emergence, and, if fertilized, oviposits on the fifth or sixth and dies immediately. If fertilization does not take place, she may survive to the ninth or tenth day. Ova and larvæ both require a very high degree of humidity. The larvæ thrive best on dried rabbit's fæces and on dried human blood. In feeding these insects in captivity the gravid females are placed in a receptacle in a globular lamp-glass standing in a Petri dish in which are placed several thicknesses of damp filter-paper spread with a quantity of rabbit fæces previously heated to 60° C. for an hour. The upper opening of the glass is closed with cotton-wool, while the space between the glass and the rim of the dish is packed with the same material; the whole apparatus is maintained at 24° C.

Repellents.—Various substances have been used on the skin with the idea of warding off these insects. Ordinary paraffin, if liberally applied to the skin, is effective. Waterston found that a substance called "*parquit*" is pleasant to use and, if well rubbed in, is efficient. Oil of citronella is also widely used for this purpose.

In preserving specimens for identification great care must be exercised. They should be placed in a web-like layer of teased cotton-wool, but must not be covered, as even slight pressure damages their appendages.

Family Simuliidæ

Small, humpbacked flies, with short legs and well-developed wings in comparison with the rest of the body. The eyes are large. The antennæ are short and straight, adorned with short hairs.

The family contains one genus, *Simulium*.

SIMULIUM (SANDEFLIES OR BUFFALO-GNATS)

These small flies are extremely voracious. Both sexes feed on mammalian blood, commonly attacking cattle and human beings in the vicinity of their breeding-places. *S. damnosum* has recently been proved to be the intermediary host of *Onchocerca volvulus* in Central Africa.

Geographical distribution.—The following species are common in various parts of the world: *S. reptans* in Europe (Fig. 340); *S. indicum*, the "potû" or "pipsa" fly of India; *S. damnosum*, the "jinja" fly of Central Africa; *S. vittatum* of North and South America. Numerous species occur in the Upper Amazon.

Life-history.—The eggs are laid in masses of 300–500 each, in water. They are triangular in shape, yellowish when fresh, but becoming black at a later stage. The larvæ emerge in two or three weeks, and immediately attach themselves to stones; they are cylindrical in shape, with a posterior swollen extremity. The pupa is attached to aquatic vegetation, and is encased in a cocoon open at the top, from which emerge a pair of branching gills.



Fig. 340.—*Simulium reptans*. × 10.

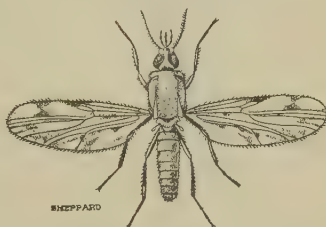


Fig. 341.—*Culicoides*, ♀. × 20.

Family Chironomidæ

These are small, delicate flies, generally known as midges. The antennæ are plumose in the male and pilose in the female, in contradistinction to the almost bare antennæ of the Simuliidæ. They are a large family, comprising over 1,000 species; the most important genera from a medical point of view are *Culicoides* (Fig. 341) and *Leptoconops*, which in many parts of the world bite man viciously.

C. austeni has recently been found by Dyce Sharp to be the intermediary host of the filaria, *A. perstans*. This insect is not only a night-biter, but will bite only in the dark and not at all by moonlight, and prefer dark skins.

Life-history.—The eggs, which are very small and oval, are laid on algæ in shallow water. On hatching, the larvæ wriggle in the mud at the bottom of the pond. Usually they are red in colour, and are known as "blood-worms." They are provided with four pairs of gills. The pupa is furnished with no exterior casing, so that the wings and legs are fused to the thorax. Two long respiratory trumpets are present, and the adult emerges after three days.

Family Brachycerous Diptera

In these flies the antennæ usually consist of three dissimilar segments, of which the third is elongated in many cases. The venation of the wings is complex; the second longitudinal vein is not forked. This section embraces the large family of Tabanidæ or "gadflies" (Fig. 342), *Hæmatopota* (Fig. 343) and the genera *Pangonia* and *Chrysops* (Figs. 344, 345).

The males of the genus *Chrysops* suck the nectar of flowers, while the females are extremely voracious, sucking the blood of men and animals.

The eggs, which are black in colour, are laid in masses of 250 each, on leaves of plants near water, where the larvæ are aquatic in their early stages, but later live in moist earth in proximity to water.

Chrysops discalis Wilkeston, 1880, is a very common species in Central America, and is the transmitter (epidemiological and experimental) of the disease known as tularæmia (p. 264).

Chrysops dimidiata v.d. Wulp. (Fig. 345), is a West African species common



Fig. 342.—*Tabanus ustus*, ♂.

Nat. size.

(Partly after Austen; by permission of Trustees of Brit. Mus.)



Fig. 343.—*Hæmatopota*, ♀.

× 2½.

(Partly after Austen; by permission of Trustees of Brit. Mus.)

at certain times of the year in Nigeria and the Cameroons, and has been proved to be the intermediary host of *Loa loa* (p. 782). In this species the face and palpi are yellow; the scutum is black with yellow stripes; the abdomen is yellow with dusky-brown tip; the legs are yellow with dark tibiæ and tarsi; the distal half of the wings is smoky.

Life-history.—The larvæ are about 10 mm. in length, and have a smooth skin; the 5th–11th segments on their ventral surface are provided with organs of locomotion which enable them to crawl about on aquatic



Fig. 344.—*Pangonia rüppellii*, ♀. × 1½.

(Partly after Austen; by permission of Trustees of Brit. Mus.)



Fig. 345.—*Chrysops dimidiata* (v.d. Wulp.), ♀. × 2½.

vegetation. The pupa, which is brownish-yellow in colour, measures about 15 mm. in length. The anterior end is provided with four round projections.

Chrysops silacea Austen, is also common in West Africa, and acts as an intermediary for *Loa loa*. It differs from the former species in having the abdomen red, or of a bright-orange colour, and the legs of the same colour with dark-brown tarsi.

Family Muscidæ. The Blood-sucking Muscidæ

GENUS GLOSSINA (Wiedemann, 1830).

In the majority of the blood-sucking Muscidæ the proboscis is a rigid stylet, adapted for piercing.

The species forming the genus *Glossina*, or tsetse-flies, are sombre-coloured, narrow-bodied insects from about 6 or 8 to 13·5 mm. long, with a thick proboscis (i.e. proboscis enclosed by the palpi) projecting horizontally in front of the head. Their wings are large, of a brownish hue, and present a venation (Plate IX, facing p. 104) which, though quite distinctive, somewhat resembles that of the warbleflies (*Hypoderma*). The most striking peculiarity in the wing is the course of the fourth longitudinal vein, which about the middle of the wing bends abruptly upwards to meet the short and very oblique anterior transverse vein; here describing a right angle, it runs obliquely downwards to meet the posterior transverse vein, and then turns upwards to reach the margin of the wing well in front of the apex.

When a tsetse is at rest its wings overlap on the back, closing over each other like the blades of a pair of scissors (Fig. 346). This resting attitude of the wings, besides giving the fly a peculiarly elongated appearance, renders it readily distinguishable from other blood-sucking Diptera with which it might be confounded, e.g. the stable-fly (*Stomoxys*) and the cleg (*Hæmatopota*).

Stomoxys is smaller in size, has short palpi not protecting the proboscis, and its wings diverge at an angle when resting. *Hæmatopota* presents prominent antennæ, and its wings are tectiform when closed, i.e. they meet together at the base like the roof of a house and diverge slightly at the tips.

In some species of *Glossina* the abdomen is crossed by sharply defined dark-brown bands, interrupted at the middle line. In the males, beneath the end of the abdomen the external genitalia form a conspicuous knob-like protuberance which renders the sexes easily distinguishable.

In this genus the palpi are long, deeply grooved on their inner sides, and closely applied to the proboscis, which they almost entirely conceal when it is not in use, the only uncovered portion being a peculiar large bulb-like expansion at the base. The proboscis consists of three parts (Fig. 347), *labrum*, *hypopharynx*, and *labium*.

The genus *Glossina* belongs to the subfamily STOMOXYDINÆ, of the family MUSCIDÆ. The nearest related genera are *Stomoxys*, *Hæmatobia* (*Lyperosia auctt*) and *Lyperosiops* (*Hæmatobia auctt*); but on account of the limitation of existing species to the Ethiopian region, their peculiar structural features (bulb at the base of proboscis, remarkable male genitalia, characteristic venation of wings) and aberrant mode of reproduction, *Glossina* presents a marked individuality.¹

The genus at present comprises nineteen species, though this number is not necessarily final, since new species are discovered from time to time. Austen arranges the genus into four groups. (See Table facing p. 824.)

Distribution.—Tsetse-flies are confined to Africa and the south-western corner of Arabia. Some species, such as *G. fusca* and *G. morsitans*, have a very wide range throughout the greater part of intertropical Africa.

¹ Prof. Newstead in 1911 introduced a classification of species of *Glossina* based on a study of the male genitalia, which in this genus are characteristic. If macerated in potash the hypopygium can be turned backwards so as to display various complicated structures, namely the superior claspers, the editum, the inferior claspers, the harpes, the juxta or penis sheath, the median process, and the connecting membrane. All these vary in shape in different groups; the median process and connecting membrane are found only in some of them.

G. palpalis is also widely distributed—from the Senegal to Angola on the west, and throughout the Lualaba-Congo system to the Victoria Nyanza, Tanganyika, and the Upper Nile at least as far north as Mvolo in the Sudan. The range of *G. auseni*, an East African species, extends from Jubaland to Zululand. *G. morsitans* ranges southwards to Bechuanaland, north-eastern Transvaal, and Zululand, and northwards to Senegambia, southern Kordofan, and southern Abyssinia. *G. swynnertoni* a species described in 1923 and concerned in the dissemination of an outbreak of sleeping sickness, is confined to the Mwanza Province, Tanganyika Territory (see p. 125). *G. longipalpis* ranges through West Africa as far north-west as Senegal and south-east to the Katanga district of the Belgian Congo. *G. pallidipes* is found throughout East Africa from Zululand to the northern boundary of British East Africa, while westward its range extends to the Katanga district of the Belgian Congo. Other species appear to be more restricted. *G. longipennis* is found in Somaliland and adjacent regions; *G. tachinoides* has a wide range in West Africa,

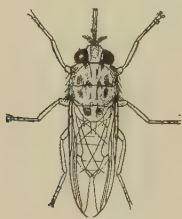


Fig. 346.
Tsetse-fly at rest.
× about 1½.

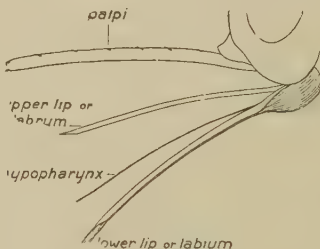


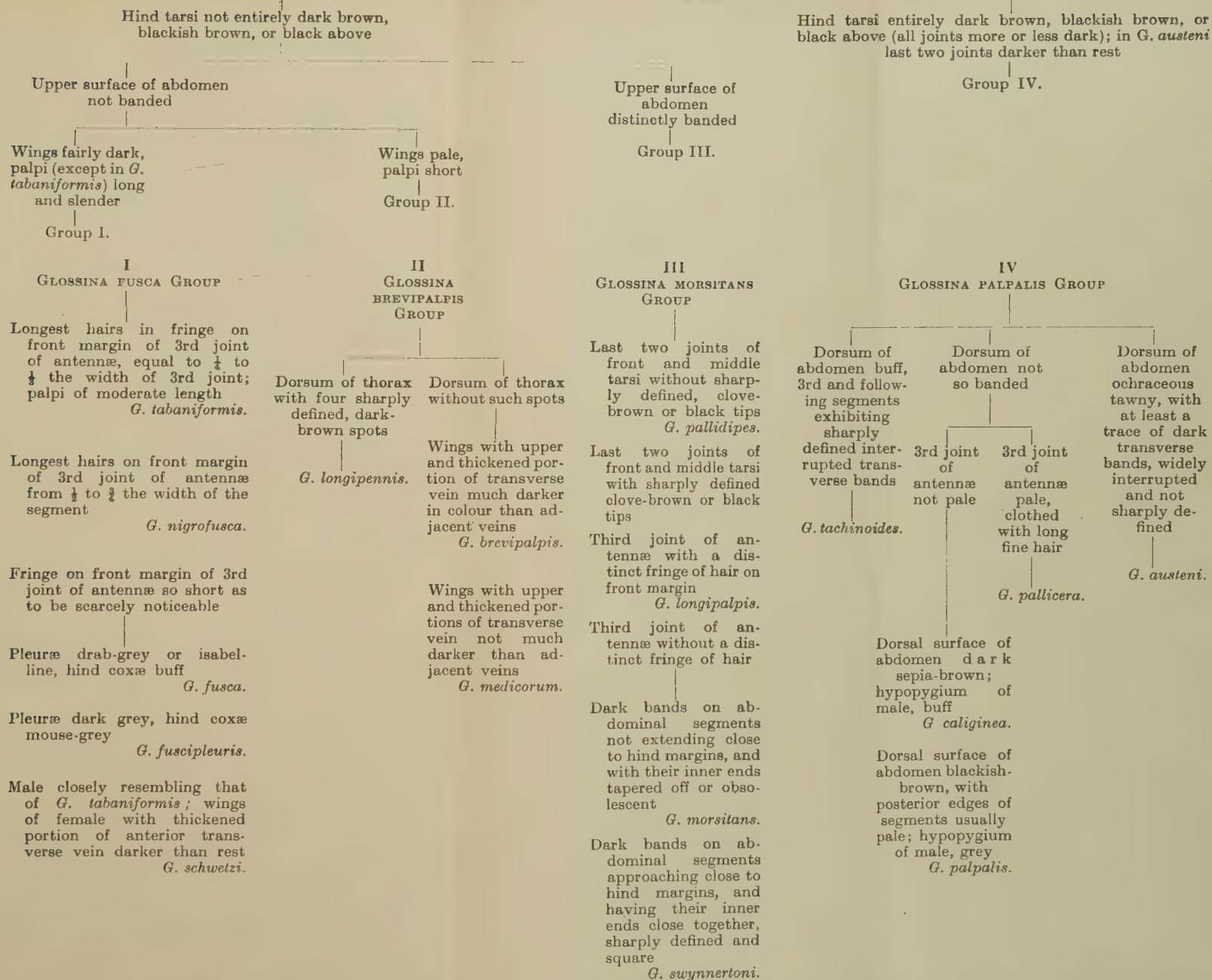
Fig. 347.
Mouth-parts of *Glossina*.



Fig. 348.
Pupa stage of *Glossina*
× 2½.

and also occurs in Southern Arabia; *G. pallicera* ranges from Sierra Leone to the Belgian Congo; *G. fusca* is found from Sierra Leone to Uganda; *G. brevipalpis* is common in South, Central and East Africa; *G. caliginea* is found in southern Nigeria. Knowledge of the topographical distribution of these flies is an important matter. The species of *Glossina* are never found on mountains; they are seldom seen above 3,000 feet; they are absent from extensive plains or other open places; and are rarely met with in close cultivation. Cover, in the nature of bush, trees, or forest, is essential, and the species of the *G. palpalis* group are usually restricted to the neighbourhood of water, being found along the banks of rivers, brooks, and springs, round the coasts of lakes, and on slow rivers and lacustrine islands. They do not as a rule frequent a sudd-covered or sedgy-banked river or lake-shore or sedgy swamp, unless continuous with a belt of trees. The members of the *G. morsitans* group, however, as well as certain other species such as *G. brevipalpis*, are far from being confined to the immediate vicinity of water. The tracts infested by tsetse-flies vary greatly in disposition and extent, according to the species concerned and the local or seasonal conditions. Thus, a so-called "fly belt" or "fly area" may be represented in one case by a narrow border of forest, but a few yards in width, along the edge of a stream; in another by a patch of "orchard bush"; or, yet again, as sometimes in the case of *G. morsitans* or *G. brevipalpis*, by a wide expanse of bush-covered or wooded country extending for many miles. It frequently happens that "fly belts"

SYNOPSIS OF GENUS *GLOSSINA*



NOTE.—*G. severini*, of which only two specimens (from Belgian Congo) are at present known, is not included in the above table, since its precise affinities are as yet uncertain; although in some respects resembling *G. fuscipleuris*, it is distinguished by relatively longer and stouter palpi, and darker and more uniformly coloured hind tarsi. *G. livingstoni*, of Cameroon, very few specimens of which have yet been captured, is closely allied to *G. fusca*, but is distinguishable externally from that species by its relatively much shorter palpi and slightly more robust appearance.

undergo enlargement during the rains and a corresponding shrinkage during the dry season, the flies extending their area of occupation in the period of maximum cover, and withdrawing again to the shelter of thicker patches of bush, or true forest, when bush fires or the withering of foliage threaten their exposure to the fierce heat of the sun.

Reproduction.—The species of *Glossina* do not lay eggs as do the majority of the Diptera, but, as in the case of forest-flies (Hippoboscidae), the eggs hatch, and the larvæ feed, develop, and moult within the body of the parent, so that when extruded they are practically ready to pupate. In fact, the extruded larva becomes a pupa (Fig. 348) within an hour or two, the larval skin becoming a dark, rigid puparium. When extruded, the fully-grown larva is nearly as large as the abdomen of the mother; it is a yellowish ovoid body composed of thirteen segments and presenting two small hooks at the anterior pole, and two respiratory protuberances at the posterior end, which is black. A female tsetse-fly deposits her larvæ singly, at intervals of about a fortnight or three weeks, invariably choosing as a nursery a shaded spot where cover for the pupating larva is available in the form of loose, dry sand, humus, or vegetable debris. The necessary facilities in this respect are frequently afforded by the ground beneath fallen trees, where tsetse pupæ or empty pupa-cases are sometimes found in considerable numbers. The perfect insect emerges from its pupa-case in about four to nine weeks.

Habits.—All tsetse-flies feed on blood, certain species, such as *G. morsitans*, exhibiting great persistency and voracity in their attacks on man and animals. The blood-sucking habit, contrary to what is the case among horse-flies (Tabanidæ), Simuliidæ, and mosquitoes (Culicidæ), is not confined to the females, but is common to both sexes. *G. palpalis*, like *G. morsitans*, is active and ready to attack throughout the day, from an hour or so after sunrise onwards. As a general rule, *G. brevipalpis*, *G. fusca*, and *G. pallidipes*, all three of which haunt by preference the edges of paths, spend the greater part of the day resting motionless on tree-trunks. Though sometimes aggressive in the early morning, *G. brevipalpis* does not usually leave its hiding-places until late in the afternoon, when it remains on the wing until about half-an-hour after sunset. *G. fusca*, a more bloodthirsty species than *G. brevipalpis*, flies more silently, and, as a rule, bites only after dark. The period of activity of *G. pallidipes*, on the other hand, is usually in the afternoon, commencing and terminating before that of *G. brevipalpis*. While *Trypanosoma gambiense* is conveyed by *G. palpalis* and *G. tachinoides*, and *T. rhodesiense* by *G. morsitans* and *G. swynnertoni*, the rôle, if any, of the other species of *Glossina* in the dissemination of human trypanosomiasis is as yet unknown.

A synopsis of the characters of the four *Glossina* groups faces p. 824.

GENUS STOMOXYS (Geoffroy, 1762)

STOMOXYS CALCITRANS Geoffroy, 1764 (Fig. 349)

This fly, which in many respects resembles the common house-fly, has a world-wide distribution. It can easily be distinguished from the latter during life by its stiff proboscis as well as by the gentle curve of the fourth longitudinal vein. *Stomoxys* may enter houses and bite man, but it usually haunts the stables and feeds on cattle and horses; in the latter, it transmits, probably mechanically, the trypanosome of "surra"—*T. evansi*.

The eggs, which resemble those of the house-fly, are deposited in horse-

dung, and hatch in two or three days. The larvæ and pupæ greatly resemble those of the house-fly.

Other blood-sucking muscidæ which may attack man are *Hæmatobia stimulans* and *Lyperosia irritans* (Fig. 350), the life-histories of which are in many ways similar to that of *Stomoxys*.



Fig. 349.—*Stomoxys calcitrans*. $\times 3$.



Fig. 350.—*Lyperosia irritans*. $\times 7$.

Muscidæ that do not suck blood

MUSCA DOMESTICA (Linn., 1758)

The common house-fly (Fig. 351) is a cosmopolitan domestic species, and, on account of its insanitary habits, acts as a vector of pathogenic micro-organisms (especially the dysentery bacillus), *Entamæba histolytica* cysts, various other protozoa, and the eggs of helminths.

The insect is dark-grey in colour, with four parallel black stripes on the dorsum of the thorax, and measures about 8 mm. in length. The eggs are laid in masses in manure and other refuse, and hatch in 24 hours in hot



Fig. 351.—*Musca domestica*, ♀
 $\times 3$



Fig. 352.—*Fannia canicularis*, ♀.
 $\times 4$.

weather. The larvæ are legless maggots bearing large stigmal plates on the abdomen (Fig. 313).

The larva grows rapidly and, under the most favourable conditions of temperature and moisture, pupates in five days. The puparium has an elongate-barrel shape, and in the tropics the pupal stage lasts about three days. The adult fly lives about a month. The larvæ are capable of

traversing considerable thickness of soil in order to reach the surface—over 3 ft.

The best method of storing manure, if it is desired to keep it, is to ram it so tight that it ferments to such an extent as to destroy the maggots.

In tropical countries house-flies are in evidence all the year round, but in dry countries they die off, or the larvæ are killed, during the period of maximum heat and drought. In temperate countries these insects die off in the winter season, and are most numerous in early autumn. The larvæ survive by lying buried in decaying matter.

A nematode worm, *Habronema muscæ*, a stomach-worm of horses, is ingested by the larvæ of *M. domestica*, either in the egg or in the larval stage. The embryo of this worm continues its development in the fly, and the final larval stage is found in the proboscis of the adult insect.



Musca domestica.



Wohlfahrtia magnifica.



Auchmeromyia luteola.



Stomoxys calcitrans.



Calliphora vomitoria.



Cordylobia anthropophaga

Fig. 353.—Stigmata of muscid larvæ, a means of rapid identification.
Magnified.

The lesser house-fly, known as *Fannia canicularis* (Fig. 352), has much the same habits as the preceding species, and can act as a facultative porter of pathogenic micro-organisms.

WOHLFAHRTIA MAGNIFICA (Schiner, 1862)

This species belongs to the SARCOPHAGIDÆ, or flesh-flies; it is 10–13 mm. in length, and of an ashy-grey colour. The head is slightly larger than the thorax, the vertex and frontal region are black, while the cheeks are satin-white, the palpi and antennæ black. The thorax is ashy-grey, with three longitudinal black stripes. The abdomen is light-grey, with three black spots adorning each segment. The legs are black.

This species is found in Russia and in southern Europe, spreading to Egypt and Asia Minor; it frequents the open country, and breeds in living in preference to dead tissues.

In man the larvæ have been found in open wounds, in the nasal fossæ, palate, and eyes.

The larvæ of these various muscid flies can be identified by the shape of their posterior stigmata. (Fig. 353.)

AUCHMEROMYIA LUTEOLA (Fabr., 1805)

A. luteola (Fig. 354) is widely distributed throughout tropical Africa. It ranges from Northern Nigeria to Natal, and has been found in the Sudan. It measures 10–12 mm. in length, and the body is rather stoutly built. The general colour is orange-buff, but numerous small black hairs give it a smoky appearance. The head is large, with eyes well separated in both sexes. The thorax shows two indistinct, dark, longitudinal stripes, which do not reach its posterior border. The abdomen differs in the two sexes, the second segment in the female being twice the length of the same in the male. The first segment has a narrow dark stripe on its posterior margin in both sexes; the second segment in the male is marked by a broader band, tapering forwards along the middle line to the base of the segment. In the female the dark band is so wide that it occupies almost the whole segment. The third segment is almost entirely black in both sexes. The fourth is dark at the base and lighter posteriorly. The legs are the same colour as the rest



Fig. 354.—*Auchmeromyia luteola*, female.

of the body. The first tarsal joint is jet-black, and stands out prominently against the large cream-white pulvillus. The wings are of a smoky-brown colour with conspicuous venation.

The larva (Fig. 355), known as the "Congo floor-maggot," is of a dirty-white colour and semi-translucent. It is in eleven segments, and grows to about 15 mm. in length. The central part of the ventral surface is flattened. At the posterior margin of each segment are three short limbs transversely arranged and provided with spines directed backwards. These enable the maggot to move about caterpillar-like and fairly rapidly. Laterally the segments bear two or more irregular protuberances, each of which has a posteriorly directed spine and a small pit. The anterior segment is roughly conical, and bears the mouth, which is placed between two black hooks protruding from its apex and curved backwards towards the ventral surface of the body. Paired groups of minute teeth are placed around the two hooks so as to form a sort of cupping apparatus. The last segment is larger, depressed, and turned upwards at an angle of about 45° with the rest of the body; two spiracles open on its dorsal surface surrounded by spines. The anus is placed in the anterior portion of its ventral surface, and behind it are two prominent spines. The alimentary canal commences with a short cesophagus which ends in a proventriculus. A remarkable dorsal diverticulum, corresponding to the food reservoir of the muscid larva, opens

into the cesophagus near its anterior end. After the larva has fed, the diverticulum is a very conspicuous object, being seen through the semi-transparent body-wall as a bright-red area, extending, when full of blood, from the head to about the fifth segment. The midgut is short; the hindgut is long, much coiled, and occupies the greater part of the body-cavity. The maggot has a thick integument, which enables it to withstand a good deal of pressure without injury.

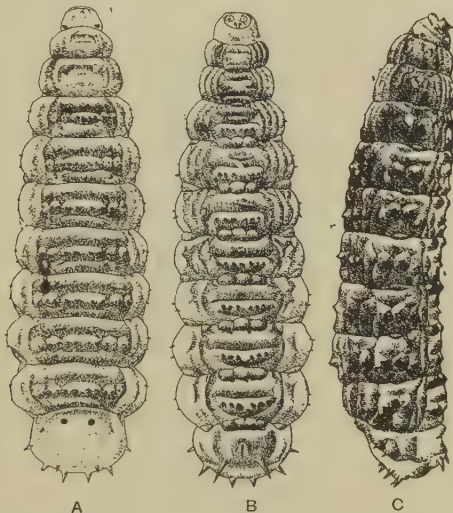


Fig. 355.—Larva of *Auchmeromyia luteola*. $\times 5$. (After Brumpt.)

A, Dorsal view; B, ventral view; C, lateral view.

The duration of the larval period has not been determined. When ready to pupate, the larva selects a suitable spot and lies dormant. The puparium is a dark reddish-brown oblong body, measuring 9–10.5 mm. in length by 4–5 mm. in breadth. The anterior end is roughly conical; the posterior is rounded. The pupa stage lasts from two to three weeks.

The fly is usually found sitting motionless among the thatch, beams, and cobwebs of the walls and roofs of native huts, but it is very difficult to see on account of its protective colouring, which corresponds exactly with the smoke-stained straw and rafters. It never bites, is usually silent, and deposits its eggs in the dust-filled cracks and crevices of the mud floors of the huts, particularly in spots where urine has been voided.

The larvæ are found especially under the mats on which the natives sleep, in the floor crevices, and in moist soft earth at a depth of 3 in. or more. They feed mainly or entirely at night, and they drop off at once if the limb on which they are feeding is moved. Those who sleep on beds or raised platforms are not attacked, as a rule, unless the bed be low, when the maggot may reach the occupant by crawling up the supports or the grass wall against which the bed is usually placed.

The larva of *A. luteola* may be recognized by the characteristic shape of the stigmata or openings of the respiratory tubes at the posterior extremity (Fig. 353).

COCHLIOMYIA MACELLARIA (Fabr., 1794) (Fig. 356)

THE SCREW-WORM.

This insect is common throughout America. It is 9-10 mm. long; it lays a mass of 300-400 eggs on the surface of wounds, and in the ears and



Fig. 356.—*Cochliomyia macellaria*, female.

nasal fossæ. From these eggs the larvæ are hatched in a few hours. The larvæ (Fig. 357) are white, about $\frac{3}{4}$ in. in length, and formed of twelve segments carrying circles of minute spirally arranged spines which give the creature a screw-like appearance. The larvæ burrow into the tissues, destroying cartilage and even bone; should the ear or nasal fossæ be attacked, the brain may be penetrated and death ensue.

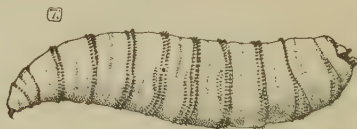


Fig. 357.—*Cochliomyia macellaria*, larva.

CHRY SOMYIA BEZZIANA (Villeneuve, 1914)

This species is found in India and in Cochin-China. It is 8 mm. in length by 13 mm. in breadth. In colour it is metallic blue; the thorax is bright green shading into blue, especially in the posterior half; the scutellum is blue.

In the *male* the eyes are reddish-brown and closely approximated; the cheeks are orange and covered with light silky hairs. The antennæ are deep orange. The abdomen is deep blue with green reflections, and the legs are black in colour. In the *female* the eyes are widely separated; the frontal stripe is broad, dark grey, and fringed with bristles. The *larva* is 12 mm. in length, yellowish-white in colour, with slightly pigmented extremities. The meso- and metathorax are encircled with a girdle of four rows of stout recurved spines. The posterior spiracles on the seventh segment are deeply placed in a horizontal slit, the anterior lip of which is well developed and provided with a pair of fleshy tubercles at each side of the middle line. The *puparium* is shorter than the larva, and of a deep mahogany colour. The *eggs* are laid in diseased tissues, and hatch in 28 hours.

The larvæ cause great destruction of tissues, as in the preceding species.

CORDYLOBIA ANTHROPOPHAGA (Grünberg, 1903) (Fig. 358)

TUMBU FLY; "VER DU CAYOR."

This species is widely distributed in Central Africa. It measures from 8.5 to 11.5 mm. in length. It is of a yellowish-grey colour, with black spots on the abdomen and with brown-coloured wings. It much resembles *Auchmeromyia luteola*, but the male *Cordylobia* is distinguished from the male of that species by the closely-set eyes. In the female *Cordylobia* the abdominal segments are of equal size, while in the female *Auchmeromyia* the second segment is of greater length than the others. The fly is usually inactive, but, when disturbed, flies with great rapidity (Blacklock and Thompson).

The eggs are laid on soil, and the larvæ (Fig. 359) on emerging are very active; they are white in colour, are visible to the eye, and wander about till they find a suitable host (dog, man, or rat). In its early



Fig. 358.—*Cordylobia anthropophaga*.

stages the larva is provided with adaptive structures, such as a cephalopharyngeal skeleton and cuticular spines, which assist it to penetrate the skin. There are three moults or instars. Development takes place in the subcutaneous tissues, and is complete in 12 days. The larva emerges from the swelling, which may be situated on forearm, scrotum, or other parts of the body, and, falling to the ground, pupates in 36 hours. The pupa has a characteristic shape with a square, truncated extremity. Pupa-cases are found in rat-burrows. The adult hatches in 10-20 days, according to the mean temperature of the locality in which it occurs.

Blacklock and Gordon have proved that in the case of the tumbu-fly a remarkable example of metazoan immunity takes place. By placing *Cordylobia* larvæ of the first instar upon guinea-pigs at the first experimental infection, 49 per cent. survived to the sixth day; whereas only 7 per cent. survived this period in all subsequent applications. Local guinea-pigs are much less susceptible to first infection than those imported from England. All this evidences a great degree of immunity acquired by previous infection; it is not a general, but a local immunity parallel to that observed by Besredka in bacterial infection. No antibodies are present in the serum of immunized animals. The immunity is at first localized in that particular area of the

skin where it was acquired ; it persists for at least three months and spreads from that area. Larvæ penetrating an immune area die within forty hours while in the superficial non-vascular layers of the skin. Immune skin grafted



Fig. 359.—Adult larva of *Cordylobia anthropophaga*. $\times 5$. (After Brumpt.)

a, Dorsal view; B, ventral view; C, lateral view.
a, Antennæ; st.a., anterior spiracle.

on a non-immune animal retains and imparts its immunity; conversely a skin-graft from a normal animal acquires immunity when planted on an immune area. Metazoan infection is not invariably accompanied by an increase in the eosinophile cells.



Fig. 360.—*Dermatobia cyaniventris*, female.

Family Œstridæ

Non-bloodsucking flies, with primitive mouth-parts, and parasitic in animals and man during the larval stages.

DERMATOBIA CYANIVENTRIS (Macquart, 1843) (Fig. 360)

"VER MACAQUE."

Geographical distribution.—This species is widely distributed throughout South America.



Fig. 361. — *Dermatobia cyaniventris*
larva : early stage.
(Blanchard.)



Fig. 362. — *Dermatobia cyaniventris*
larva : later stage. (After Brauer.)

The larva occurs in the most diverse animals. It is found commonly in cattle, pigs, and dogs, but it occurs in the agouti, in the jaguar, in various monkeys, and in birds. It is rare in the mule, and writers have commented upon its absence from the horse. In man it has been reported from various

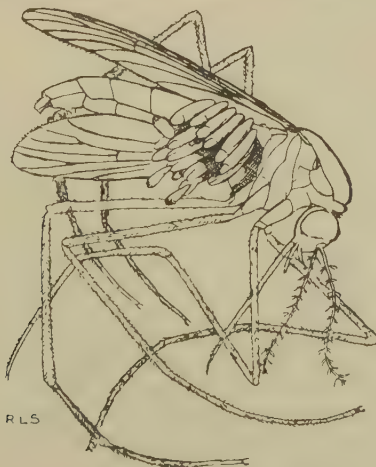


Fig. 363. — *Janthinosoma lutzi*, carrying eggs of *D. cyaniventris*
(By courtesy of Tropical Diseases Bureau.)

regions of the body, namely, head, arm, back, abdomen, scrotum, buttock, thigh, axilla. Its presence is accompanied by excruciating pains, especially at those times when the larva is moving.

At an early stage the larva has the appearance represented by Fig. 361 ;

at a later stage that represented by Fig. 362. The former stage is known as *ver macaque*; the latter, much the larger, as *torcel* or *berne*. At one time the larval stage of the same insect was erroneously supposed to belong to different species. Light has been thrown on the way this myiasis is acquired. On attaining maturity *D. cyaniventris* lays its eggs on damp leaves in damp places, the haunts of a species of mosquito, *Janthinosoma lutzi* (Fig. 363).

The packets of eggs are enclosed in a cement which, on becoming softened by moisture, adheres to the insect's thorax, and the eggs are thus conveyed to man or other vertebrates when it next commences to feed.

When hatched out, the larvæ penetrate the skin and produce an inflamed swelling about the aperture of entrance, from which a sero-purulent fluid, containing the black fæces of the larvæ, exudes.

RHINCESTRUS PURPUREUS (Brauer, 1858)

This is a small species, 8-11 mm. in length, of a deep-brown-purple colour, the body being covered with numerous coarse tuberculations. The thorax is adorned with glossy black bands.

The abdomen is iridescent in colour, purplish silver or grey, slightly shaggy at its blunt posterior extremity.

This species preys upon horses, laying its numerous eggs in the eyes or the nares. On hatching, the larvæ penetrate the nasal cavity, the frontal sinus, the pharynx, and even the larynx.

It is a common fly in southern Europe and Algeria, where it occasionally attacks man (p. 617).

ORDER ANOPLURA, OR LICE

Lice are small, flattened, thin-skinned insects without wings, with mouth-parts adapted for sucking, and an indistinctly segmented thorax. Metamorphosis is incomplete. The number of abdominal segments ranges from six to nine, the last of which is bilobed. The abdomen of the male ends bluntly and bears a spine-like penis; the spiracles are very prominently situated on the sides of the abdominal segments. The eggs, or nits, adhere to the hairs of the host, and the newly-hatched young are small editions of their parents. The species which is parasitic on man is known as *Pediculus humanus*, of which there are two varieties, the head-louse, "*P. capitis*," and the body-louse, "*P. corporis*" (some regard them, indeed, as forming but one species). (Fig. 364.) The third species is *Phthirus pubis*, the "crab-louse"¹ (Fig. 365), which lives in the genital and inguinal regions. It is distinguished from other lice by its broad, flat body and by a line of three spiracles situated on each side of the second abdominal segment. The abdomen, of six segments, is festooned. The first pair of legs are more slender than the other two; the second and third have massive talon-like claws, the thumbs of the tibiæ being prominent. The phthirus, when adult, clings to two approximated hairs, generally about 2 mm. apart, the span between the hind-legs being about that distance. The young crab-louse passes through three moults before attaining maturity. The life-cycle is complete in 27 days. When removed from man the crab-louse dies in 42 hours. Infection with this louse occurs most frequently during coitus.

In *P. humanus capitis* and *corporis* the life-history is similar. The eggs

¹ This species was originally placed in the genus *Pediculus* from which it was removed to *Phthirus* by Leach in 1815.

hatch in from eight days at 32° C. to five weeks at a low temperature, and the young louse begins to suck blood at once. The immature louse moults three times before becoming mature; the final moult into the adult form takes place twelve days after hatching. Each adult female louse lays 8-12 eggs daily, while the total life-span of such an individual is from four to six weeks. These insects cannot live for any length of time upon discarded clothing, but under experimental conditions they live longer apart from the body at low temperatures; at 40° C. they survive twelve hours, and at 5° C. ten days.

Infection occurs through contact or close association with verminous persons. Spread is greatly favoured when men sleep huddled together.

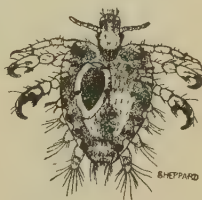


Fig. 364.—*Pediculus humanus*.
× 5. (After Bruce Cummings; by permission of Trustees of Brit. Mus.)

Fig. 365.—*Phthirus pubis*, ♀, showing contained ovum.
× 12.

A, *P. humanus*, ♀.
B, *P. humanus* var. *capitis*, ♀.

Prevention consists in personal cleanliness, removal of hair, and frequent change of clothing.

For the destruction of lice in clothing on a large scale, the most efficient method consists in the application of dry or moist heat. Both lice and nits are destroyed by a moderate degree of dry heat, 55° C. for 5 minutes, 65-70° C. for 1 minute. For practical purposes, clothes should be exposed to 70° C. for 30 minutes. Disinfection is best effected in hot-air huts. These measures may be supplemented by insecticide solutions, of which a 5-per-cent. crude carbolic solution containing soap is about the best; it may be used for leather and articles of clothing liable to be injured by heat. As a louse preventive, crude unoxidized naphthaline powder, as effective as N.C.I. and cheaper, may be dusted into the seams and renewed twice a week. Nearly all forms of treatment designed to kill lice upon the person aim at destroying the adult and immature insects, but do not destroy the nits or eggs. Chloroform water (5 : 1,000) rubbed on the infected scalp or body quickly stupefies all the living lice and renders their removal easy, but leaves nits unaffected. The removal of nits from the hair is facilitated by vinegar or acetic acid (10-per-cent.).

Apart from their unpleasant habits, lice are of medical interest, since they act as intermediary hosts or transmitters in relapsing fever, typhus, trench fever, and possibly other diseases as well.

ORDER HEMIPTERA, OR BUGS

Bugs have two pairs of wings; both pairs may be membranous, or the front pair may have the basal half thickened to form a wing-sheath. The

mouth-parts are adapted for sucking and piercing. Metamorphosis is incomplete. This order includes a number of plant-bugs and the Cimicidæ or *bed-bugs*, which are temporary ectoparasites on man, and in which the wings are rudimentary. The mouth-parts are characteristic. The labrum forms a segmented proboscis which, in repose, is bent under the head; there are no palps. The mandibles and maxillæ are provided with bristles near the tip, and it is with these that the bug obtains blood. The former are grooved along their opposed surfaces to form two channels, one for the saliva which is secreted, while the blood is haustellated along the other. The three thoracic segments are distinct; the prothorax is free and the mesothorax produced posteriorly to form a scutellum. The abdomen is flattened dorso-ventrally. The odour emitted by bugs is secreted by certain glands which open on the sternum of the last thoracic segment. The sexes are separate, the male being distinguished from the female by the more elongated abdomen and by a notch on the fourth segment of the latter, known as the organ of

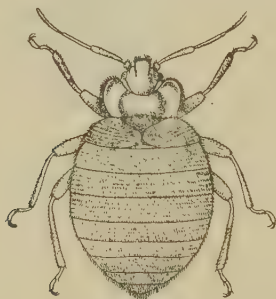


Fig. 366. — *Cimex lectularius*. $\times 7$.

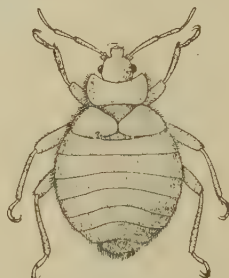


Fig. 367. — *Cimex hemiptera* (*rotundatus*). $\times 6$.

Berlese. The species parasitic on man are *Cimex lectularius*, the bed-bug of Europe, and *C. hemiptera* (*rotundatus*), the bug of warm countries, which can be distinguished by its more elongated, narrower abdomen, and by the greater dorsal convexity of the pronotum. (Figs. 366, 367.) In West Africa a species of another genus occurs, *Leptocimex boueti*, which also attacks man. The European species is thought to carry the spirochæte of relapsing fever as the recent experiments of Rosenholz (1927) seem to show. During the day the insect hides in a crevice, and at night sallies forth to suck blood.

The eggs are white and oval, cohering together in clumps; each egg has a lid through which the larva emerges, resembling its parents in general appearance, but white in colour, and having no elytra or rudimentary wings.

The most effective method of destroying bed-bugs in a building is fumigation with sulphur or, better still, with hydrocyanic-acid gas; the latter, being dangerous, can only be carried out by some skilled person. For articles of furniture which cannot be subjected to boiling water an emulsion of petroleum, made up with 3 parts of soap to 15 of hot water, to which, while still hot, 70-100 parts of oil are added, should be forced into all cracks and crevices with a brush.

Family Reduviidæ

This family includes a number of species which feed on human blood, inflicting painful bites. They are classified into three genera, *Triatoma*, *Erathyrus*, and *Rhodnius*, the members of which are for the most part confined to America, from 41° N. to 41° S., while one (*T. rubrofasciata*) has a cosmopolitan distribution.

In nature they live entirely on wild animals, frequenting their nests or burrows, but certain species have become domesticated in modern human habitations. The adults of both sexes can fly for considerable distances, but the larvæ or nymphs are flightless, and can only bite human beings in their immediate vicinity. When engorged with blood after a feed, these insects void from the cloaca a white or dark-coloured fluid into the site of the bite, a circumstance which explains the manner in which *Trypanosoma cruzi* is transmitted. Two weeks after hatching, the females lay eggs which, in the case of *Triatoma* and *Erathyrus*, are deposited singly.

The larvæ, on emerging, engorge themselves with blood on four occasions, undergoing a moult after each; they then become nymphs, which, after several feeds, moult for a fifth and final time before becoming adult. The whole cycle of evolution takes three or four months to complete.

The life-span is on an average one of three months, and when once infected with *T. cruzi* the insects remain so for the remainder of their lifetime.

GENUS TRIATOMA (Wolf, 1802)

Synonym.—*Conorhinus* Laporte, 1832.

This genus is distinguished by its smooth body and elongated or conical head.



Fig. 368.—*Triatoma megista*. Nat. size.

T. megista (Burmeister, 1835)—Brazil—is a domestic species measuring 3 cm. in length. The body is black, with red stripes. (Fig. 368.) The insect has feeble powers of flight. The life-cycle takes a year to complete, and the adults can live about six months.

T. chagasi Brumpt and F. Gomes, 1914—Brazil—has a characteristic red band on the head, and lives in the burrows of *Cherodon rupestris* and those of armadillos.

This species has been found infected with *T. cruzi* at a considerable distance from human habitations (p. 127).

T. dimidiata (Erichson, 1843)—Brazil, Venezuela, British Guiana, and San Salvador—is also naturally infected with *T. cruzi*, and possibly conveys the human disease in San Salvador.

T. geniculata (Latreille, 1811)—Paraguay, Brazil, Peru, Venezuela, and French Guiana—is a sombre-coloured species, living normally in armadillo burrows; it transmits *T. cruzi* to these animals.

T. infestans (Klug, 1834)—South America—is a domestic species and lives in cracks in the walls of houses or hen-roosts. It is found naturally infected with *T. cruzi* in Argentina.

T. protracta (Uhler, 1894)—the United States, from Utah to California—

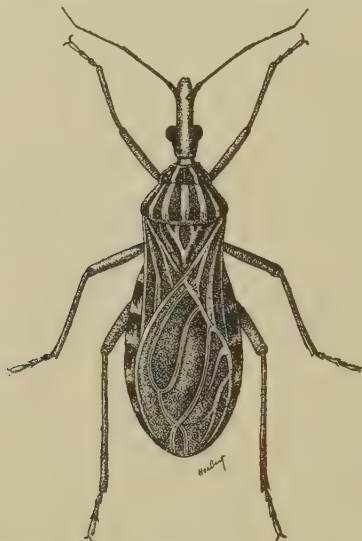


Fig. 369.—*Rhodnius prolixus*, adult male. $\times 2\frac{1}{2}$. (After Brumpt.)

is known as the "kissing bug," and lives in the burrows of rodents. Under natural conditions it harbours a trypanosome, *T. neotomæ*.

T. rubrofasciata (de Geer, 1773), a cosmopolitan domestic species, can be infected experimentally with *T. cruzi*. It has been suspected, on rather imperfect evidence, of transmitting kala-azar in India.

T. sanguisuga (Lecomte, 1855)—United States—is a common domestic species which associates with bed-bugs. Under experimental conditions it can be infected with *T. cruzi*.

T. sordida (Stal, 1859)—Brazil, Bolivia, and Paraguay—is a small domestic species met with near the banks of the large rivers; it has been found naturally infected with *T. cruzi*.

T. vitticeps (Stal, 1859)—Brazil—is the largest known of these insects, and is a rare species.

GENUS ERATHYRUS (Stal)

Erathyrus cuspidatus Stal, 1859—Venezuela—is believed to be a rare species, occurs at an altitude of 4,600 feet, and appears to be naturally infected with *T. cruzi*.

GENUS RHODNIUS (Stal, 1850)

This genus is characterized by a narrow attenuated head and 1y elongated antennæ (Fig. 369).

Rhodnius prolixus (Stal, 1859)—Venezuela, Colombia, Guiana, Brazil, and San Salvador. This species has nocturnal habits, and feeds voraciously on human blood. (Fig. 369.) Normally it lives in the burrows of the armadillo and those of a rodent (*Cælogenus subniger*).

The adult is capable of flying considerable distances; the larvæ and nymphs live in cracks in the walls and in the crevices of palm trees.

Under experimental conditions this species can transmit *T. cruzi*.

ORDER SIPHONAPTERA, OR FLEAS

Fleas are small insects with a laterally compressed body. They are wingless, and their mouth-parts are adapted for piercing and sucking. Some suck blood indiscriminately, but the majority restrict themselves to one definite host and are active ectoparasites of mammals and birds. (Figs. 370, 371, 372.) In one family, *Tungidæ* (*Sarcopsyllidæ*), or "chiggers," the females eventually attach themselves to their host as fixed parasites, embedding themselves in the skin when pregnant. (Fig. 374.)

The body is divided into head, thorax, and abdomen. The head is small compared with the abdomen, and is conical in shape, with sometimes a comb of teeth on the cheek, or on the lower edge of the head. Eyes may or may not be present. The head is provided with short antennæ lodged in definite grooves. The mouth is furnished with appendages maxillæ and palps, which conceal the other parts. The thorax is composed of three segments, which are quite independent. Each consists of a dorsal arc carrying one or more belts of bristles. In some species the pronotum, or tergum of the first thoracic segment, carries a comb on its posterior border. The three pairs of legs are composed of a number of segments, the coxa being especially long and broad. The number and character of the bristles of the joints of the legs are used for distinguishing species. The abdomen is composed of ten segments; on the ninth the tergum is in a great part occupied by a pitted sensory plate called the *pygidium*. In the male large claspers are present. Bristles project over and beyond the pygidium on the seventh segment, and are known as antepygidial bristles. There is a large and complex penis.

The female flea is larger than the male. The curved receptaculum seminis is a conspicuous object.

The eggs are dropped by the female casually, and hatch in three or four days in summer-time.

The larva lives in dust, is an active footless maggot, of a whitish colour, is sparsely hairy, and lives on faecal matter. (Fig. 373.) When full-grown it spins a cocoon and pupates. The duration of the pupal stage depends on the temperature. The pupæ are similar to the adult, and are encased in a cocoon. According to Barcroft, in the tropics fleas die out at a height of 14,000 feet.

Fleas act as mechanical carriers of disease, and also as intermediary hosts of parasites. The common dog-flea and the rat-flea harbour the cysticercus of certain tapeworms (*Dipylidium caninum* and *Hymenolepis diminuta*); but their most important rôle is as carriers of the plague bacillus from rats to man. In 1914 Rothschild pointed out that three species of *Xenopsylla* are ectoparasites of the rat in India. It is practically impossible to make out the distinguishing features of these three species unless the specimens are suitably prepared. With the aid of a hand-lens, the females can be recognized by the shape of the spermatheca after the soft parts have been dissolved by caustic potash, or

rendered transparent by means of a clearing agent. For the certain identification of the *males*, a compound microscope is necessary, when it can be seen that the ninth sternite ends in a sharp point, instead of a flattened projection,



Fig. 370.—*Ctenocephalus canis*, male.
× 16.
(Major T. L. Bomford, I.M.S.)



Fig. 371.—*Xenopsylla cheopis*, male.
× 16.
(Major T. L. Bomford, I.M.S.)



Fig. 372.—*Pulex irritans*—A, male, × 25; B, female, × 14.
(Major T. L. Bomford, I.M.S.)

as in *cheopis*. The shape of the claspers differs in *astia*; they are more elongated. These differential characters can only be relied upon in the case of fleas from the Indian area, because in that country only these three species exist.

After a short preliminary treatment with caustic potash, the fleas are treated with alcohol and xylol and placed overnight in a thin solution of balsam in xylol. Slides are prepared by coating the specimens with a thin layer of balsam and allowing them to dry overnight in the incubator. The



Fig. 373.—Larva of *Xenopsylla cheopis*. Magnified.
(After Bacot and Ridgway, "Parasitology.")

fleas themselves are mounted and orientated on the slide; the insects can then be individually examined under the microscope in rows of five each.

The presence of fleas in houses is chiefly due to want of cleanliness, especially the accumulation of dust, the proximity to hen-runs or stables, and free access of flea-carriers—cats, dogs, rats, and mice.

To rid cats and dogs of these insects they should be washed with carbolic



Fig. 374.—*Tunga penetrans* (*Dermatophylus penetrans*, *Sarcopsylla penetrans*)
—A, male; B, female. $\times 38$. (Major T. L. Bomford, I.M.S.)

soap or a strong lather of "vermijelli." Cats that object to water may be powdered with naphthaline or dusted with pyrethrum. The floors of the house should be washed with a solution of naphthaline or benzene. An emulsion of petroleum which will kill fleas when diluted with water, 1:20 or more, may be made from soft soap and ordinary petroleum, 3 parts of

soap being melted by heat in 15 of water, and 70-100 parts of oil added while still hot, with much shaking and stirring. The final mixture should be white and creamy.



Fig. 375.—Diagnostic characters of *Xenopsylla* rat-fleas. Magnified.
(After Cragg and Hirst.)

1. *X. astia*: pygidium of ♂; 1a, pygidium and spermatheca of ♀. 2. *X. braziliensis*: pygidium of ♂; 2a, pygidium and spermatheca of ♀. 3. *X. cheopis*: pygidium of ♂; 3a, pygidium and spermatheca of ♀. Note shape and size of spermatheca.

The irritation of flea-bites may be allayed by the application of 1:20 carbolic, or the following ointment:

Ac. carbol.	℥ x.
Menthol	gr. v.
Zinc oxide	℥ i.
Adipem. prep. ad.	℥ i.

or	Hyd. ammon.	.	.	.	gr. x.
	Liq. pic. carb.	.	.	.	℥ i.
	Ung. paraff. B.P. ad.	.	.	.	℥ i.

XENOPSYLLA ASTIA (Rothschild, 1911)

In the *male* the antepygidial bristle is similar to that of *X. cheopis*, and is easily differentiated by the shape of the ninth sternite, which, instead of being club-shaped, has the appearance of a ribbon, due to the chitinization of the ventral margin. The outer flap of the organs of copulation is narrower than in *X. cheopis*, and bears fewer bristles.

The "tail" of the receptaculum is so strongly widened near the constriction that it is much wider than the "head." The eighth segment has more than 30 bristles on its outer surface. (Fig. 375, 1.)

XENOPSYLLA BRAZILIENSIS (Baker, 1904)

In the *male* the long dorsal bristle on the seventh abdominal segment in front of the pygidium is placed on a long pedestal. In the *female* the "head" of the receptaculum seminis is very much wider than the "tail." (Fig. 375, 2.)

XENOPSYLLA CHEOPIS (Rothschild, 1903)

In the *male* the ante-pygidial bristle is situated on a short pedestal. The outer flap of the copulatory organs is sole-shaped; its upper edge is more curved than the lower, and bears 9 or 10 bristles on its outer surface, all of them thinner than in *X. braziliensis*, and drawn out into a long, thin point. The ninth sternite has the appearance of a club, the upper side of which is flattened.

In the *female* the "tail" of the receptaculum is much longer than in the preceding species, and, near the constriction, is distinctly wider than the "head." (Fig. 375, 3.)

V. MEDICAL HERPETOLOGY

A SYNOPSIS OF THE VENOMOUS SNAKES

(By JOAN B. PROCTER, F.Z.S., F.L.S., Curator of Reptiles to the Zoological Society of London)

SNAKES form a suborder of Squamata, the order of Reptilia which comprises the Lizards (Lacertilia) and the Snakes (Ophidia).

Snakes all have the following characters, some but never all of which are also found in the Lizards:—

Quadrato bone articulated to the skull; no tympanic cavity; an osseous brain-capsule; mandibles united mesially only by highly elastic ligament.¹ Limb girdles absent, or reduced to vestiges of the pelvic, as in the Pythons,² etc. No movable eyelids, the eye being covered with a transparent disk, which is shed with the rest of the epidermis. Tongue deeply bifid, retractile into a basal sheath; protrusible when the mouth is closed, through a notch in the rostral shield.³ Anal cleft transverse, as in lizards.

About 2,000 species are known, and these are specialized to all conditions of life. Some are minute, blind, burrowing, and worm-like; some powerful constrictors reaching 30 ft. in length; some slender tree-snakes; and there are also fresh-water or marine species of entirely aquatic habits. They may be diurnal or nocturnal in habits, oviparous or viviparous, venomous or non-venomous, gentle or savage.

The only kinds dealt with in the present section are those the bites of which are known to be dangerous to man, and these belong to but two out of the nine families into which snakes of the present day are grouped, viz. Colubridæ and Viperidæ.

The poison apparatus (Fig. 376).—Snakes do not sting, as is sometimes supposed. The poison apparatus consists of a pair of venom-secreting glands, connected by ducts to the poison-fangs in the maxillæ. These glands, which are situated in the temporal regions, are operated by the act of biting, when the gland is squeezed by the contraction of the temporal muscle, the venom being expelled in this way into the wound by means of the grooved or tubular fangs. In one or two of the cobras the venom is expelled with such force that it is ejected in a stream when the snake is angry, this jet being aimed at the face of the enemy, and causing temporary or permanent blindness. These are known as "spitting" cobras, and are only found in Africa.

The venom, a clear, amber-coloured fluid, is composed of modified proteins, the separate toxic principles of which are not perfectly known.

¹ This character alone separates them from the Lizards.

² In pythons and boas the hind-limbs are present in a vestigial stage, showing externally as "claws," which are more pronounced in the males.

³ In the sea-snakes this notch is paired, and only the bifid portion of the tongue passes in and out.

The venom is of two kinds: that of the family Viperidæ (Vipers) acts principally upon the vascular system, and that of the subfamilies Elapinae

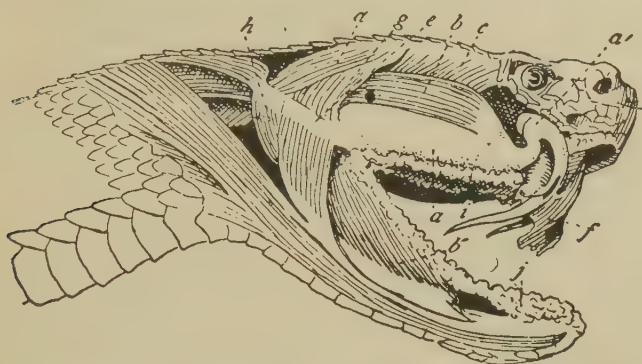


Fig. 376.—Poison apparatus, venom gland, and muscles of rattlesnake (lateral view). (After Duvernoy, in Boulenger's "Snakes of Europe.")

a, Venom gland; *a'*, venom duct; *b*, anterior temporal muscle; *b'*, mandibular portion of same; *c*, posterior temporal muscle; *d*, digastric muscle; *e*, posterior ligament of gland; *f*, sheath of fang; *g*, middle temporal muscle; *h*, external pterygoid muscle; *i*, maxillary salivary gland; *j*, mandibular salivary gland.

and Hydrophiinae (Cobras and Sea-snakes) acts on the nervous system and causes respiratory paralysis. (See pp. 609-612.)

The venom-gland has been evolved from the parotid, and the solid maxillary teeth have become first grooved, and finally tubular fangs. Some harmless solid-fanged snakes secrete venom to some extent in their parotid glands, showing the first stage in the evolution of a poison apparatus.

Locomotion.—The locomotion of snakes is effected only to a limited extent by the flexibility of the ribs, the free ends of which are in this case used to crawl with. The swift darting and slow winding movements are produced almost entirely by the muscles, aided by the gripping action of the skin. Sea-snakes have additional assistance from their tails, which are compressed into a powerful oar.

Characters used for identification.—Osteological and dental characters are used to determine families and genera, and it is therefore necessary to understand the various types of ophidian skulls and the different arrangement of fangs and solid teeth. For generic and specific distinctions the form and number of the shields and scales are also of great importance, and the special names of these should be memorized.

The *head-shields*, when not broken up into small scales, are regularly arranged; they are named in Fig. 377.

Lepidosis (Fig. 378) is next considered; the dorsal scales are counted from side to side, and their form noted. They may be straight or oblique, keeled or smooth. The ventral plates are counted from chin to anal cleft. The subcaudals, which may be single or paired, are also counted, and the anal plate (the ventral shield covering the anal cleft) examined.

In the following keys the more obscure skeletal or detailed dental characters will not be used, and only those explained here need be studied.

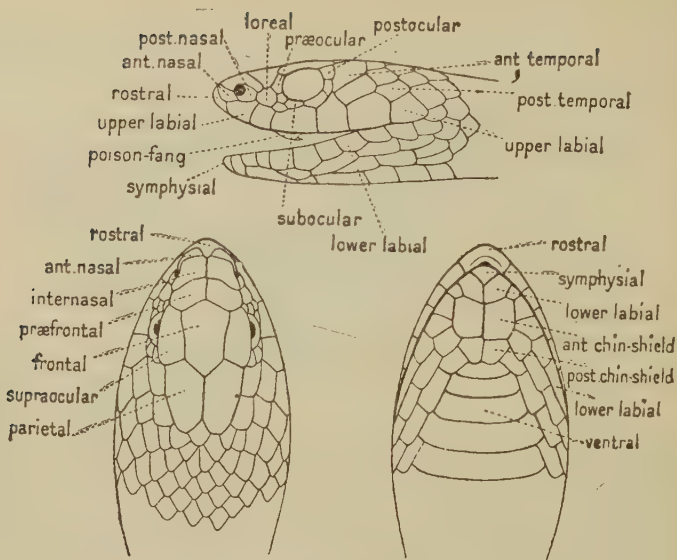


Fig. 377.—Head-shields of *Causus rhombeatus*. (After Boulenger, "Proc. Zool. Soc.," 1915.)

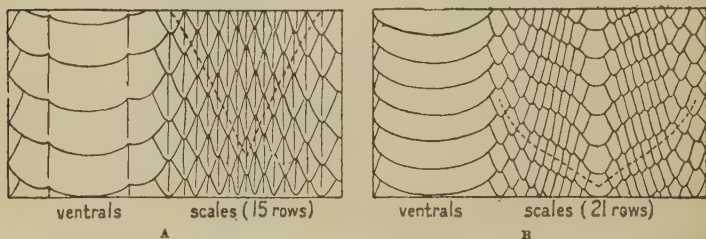


Fig. 378.—Scaling of thickest part of body. (After Boulenger, "Proc. Zool. Soc.," 1915.)

A, *Gastropyxis smaragdina*, with keeled, straight scales and bicarinate ventral shields. B, *Boiga* *C. blandingii*, with oblique scales, enlarged vertebrals, and simple ventral shields.

SYNOPSIS OF FAMILIES

- Worm-like, with small inferior mouth; eyes hidden or just visible under the head-shields. Cycloid scales.

A. Maxillæ toothed, mandibles toothless, tail usually not much longer than broad.

TYPHLOPIDÆ.

B. Maxillæ toothless, mandibles toothed, tail often long.

GLAUCONIDÆ.

II. Mouth large, eyes exposed.

A. Vestiges of limbs.

1. Ventrals hardly enlarged. Small burrowing snakes with short tails. ILYSIIDÆ.
2. Ventrals narrower than the body, but definitely enlarged. Constricting snakes of all sizes and forms. BOIDÆ.

B. No vestiges of hind-limbs.

1. Præmaxilla toothed. XENOPELTIDÆ.
2. Præmaxilla toothless, maxillæ horizontal.
 - a. Ventral shields small.
 - a Small burrowing snakes, restricted to India; eyes minute, in an ocular shield, tail short, usually ending in a highly specialized scute. UROPELTIDÆ.
 - b. Ventral shields as wide as the body.
 - a Pterygoid not reaching quadrate or mandible, maxillæ curved inwards, no mental groove. AMBLYCEPHALIDÆ.
 - β Pterygoid reaching quadrate or mandible, or a mental groove. COLUBRIDÆ.
 - * All maxillary teeth solid. Colubridæ series A. Aglypha.
 - ** Posterior maxillary teeth grooved. Colubridæ series B. Opisthoglypha.
 - *** Anterior maxillary teeth grooved or tubular. Colubridæ series C. Proteroglypha.
3. Præmaxilla toothless; maxillæ vertically erectile, with enormously enlarged tubular fangs anteriorly. VIPERIDÆ.

COLUBRIDÆ

This, the largest family, is divided into three groups, according to dentition:—

- I. AGLYPHA, in which the poison apparatus is absent, comprising many hundreds of harmless snakes.
- II. OPISTHOGLYPHA, in which the apparatus is present, and the fangs are situated behind the other maxillary teeth. The majority of these snakes are not dangerous to man.¹
- III. PROTEROGLYPHA, in which the apparatus is highly developed, and the fangs, usually much enlarged, are in front of the solid maxillary teeth.

¹ As the vast majority of the snakes of this series are not dangerous, Opisthoglypha are not dealt with here. Serious accidents have happened, however, through the bites of the well-known South African "Boomslang" *Dispholidus* and other Dipsadomorphine snakes. Cases of snake-bite from large back-fanged forms should be treated as Elapine poisoning for all practical purposes.

The series Proteroglypha (the Cobras, Sea-snakes, etc.) is divided into two subfamilies, as follows:—

1. Tail compressed into an oar (Sea-snakes). **HYDROPHIINÆ.**
2. Tail cylindrical (Land-snakes, Cobras, etc.). **ELAPINÆ.**

The second subfamily is easily recognized, but in distinguishing Elapines (Fig. 379) from harmless Colubrines it is useful to remember that, besides the form and situation of the poison-fangs, the loreal shield is constantly absent. This is especially useful in the case of the Coral Snakes of North America, where many harmless species resemble them closely.

HYDROPHIINÆ

The Sea-snakes are strictly marine,¹ often being caught far out at sea, although it is more usual to find them near the coast, or in rock-pools or estuarine waters. They are mostly viviparous, and feed upon fish and crustaceans.

Their venom is deadly to man, that of *Enhydrina schistosa*, a common species, being more active even than that of the Kraits (*Bungarus spp.*) or Cobras (*Naja spp.*).

Geographically, they are confined to the Indian and Pacific Oceans, their principal range being the tropical Indo-Australasian region from the Persian Gulf to Queensland. They are most common in the Malay Archipelago, and are not found on the East African shore of the Indian Ocean, although the Common Black and Yellow Sea-snake (*Pelamis platurus*), which has a wider range than the rest, is found in South African waters.

SYNOPSIS OF HYDROPHIINÆ²

Indo-Australasian Coasts

- I. Maxilla extending forward beyond the palatine; ventral shields large.
 - A. Nostrils superior; nasal shields in contact.
 - a. 5 to 11 maxillary teeth. **AIPYSURUS.**
 - b. No solid maxillary teeth. **EMYDOCEPHALUS.**
 - B. Nostrils lateral; nasal shields separated by inter-nasals. **LATICAUDA.**
- II. Maxilla not extending forward beyond the palatine; ventrals small or absent.
 - A. Symphysial shield triangular, not concealed in a mental groove.
 1. Ventral shields not distinct from lateral scales.
 - a. Nostril in the nasal shield. **PELAMIS.³**
 - b. Nostril between two nasals and the prefrontal. **ACALYPTOPHIS.**
 - c. Nostril between two nasals and an internasal. **THALASSOPHIS.**

¹ With the exception of one species of *Hydrophis*, which lives in a lake in Luzon.

² For a detailed synopsis see M. A. Smith's monograph on "Sea-snakes," Brit. Mus. N. H., 1926.

³ Also found in South African Waters.

2. Ventral shields distinct at least on the anterior part of the body.

- a. No præocular; body moderately long. HYDRELAPS.
- b. Præocular present; body very long. HYDROPHIS.¹
- c. Præocular present; body short, stout.
The last² three or four rows of scales enlarged. LAPEMIS.

B. Symphyseal shield narrow, half-concealed in a mental groove.

Scales imbricate; ventrals very small but distinct.

ENHYDRINA.

ELAPINÆ

The geographical distribution of this subfamily is interesting, and very different from that of the Vipers.

Only one genus occurs in America, namely *Micrurus* (syn. *Elaps*), comprising the Coral Snakes.

In Africa the majority of the hooded Cobras are to be found, including those which spit their venom in a stream directed at the eyes of their opponents. Another well-known African genus is *Dendraspis*, comprising the Mambas or Tree-cobras.

In Persia and Iraq a hoodless Cobra, *Naja morgani*, is found. Eastward to China the Spectacled Cobra (*Naja naja*), the Hamadryad or King-Cobra (*Naja lannah*), and Kraits (*Bungarus spp.*) are the most common.

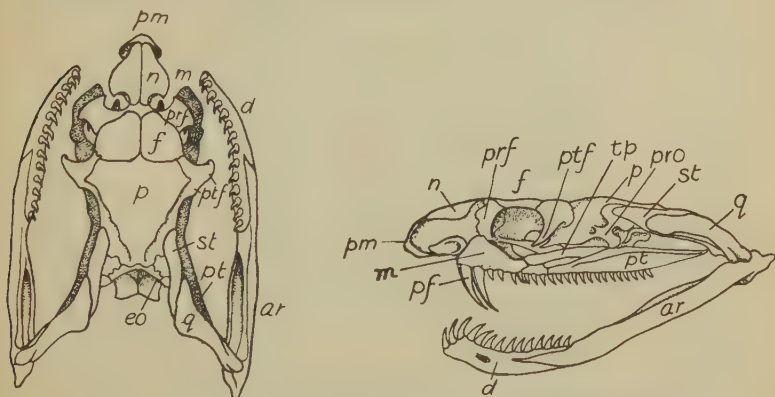


Fig. 379.—Skull of *Naja tripudians*, upper view and side view.

(After Boulenger, "Catalogue of Snakes," vol. iii.)

ar, Articular; d, dentary; eo, exoccipital; f, frontal; m, maxillary; n, nasal; p, parietal; pf, poison-fang; pm, præmaxillary; prf, præfrontal; pro, prootic; pt, pterygoid; ptf, postfrontal; q, quadrate; st, supratemporal; tp, transpalatine.

The Australian region, including the island groups from Java to New Guinea, is the home of the Elapines, where thirty genera, all more or less closely related, are found. In Australia itself they are more numerous than the harmless snakes which inhabit these territories. Two of these genera are particularly misleading to the novice, as they resemble Vipers in every

¹ This genus now includes the formerly distinct *Distira*.

² i.e. the longitudinal rows nearest the ventrals on each side.

outward character. There are, however, no True Vipers in this region, so that any heavy viper-like snake with large anterior fangs may be sought in the key to the Elapine genera.

SYNOPSIS OF ELAPINÆ

I. *African Genera*

A. Maxillary bones not extending forward beyond the palatines.

1. Head not distinct from neck.

a. Scales not oblique, subcaudals 65-80. BOULENGERINA.

b. Scales more or less oblique, subcaudals 12-25. ELAPECHIS.

B. Maxillary bones extending forward beyond palatines.

1. Neck dilatable, scales oblique.

a. Head distinct from neck, rostral not prominent, subcaudals 50-75. NAJA.

b. Head not distinct from neck, rostral prominent, subcaudals 30-50. SEPEDON.

2. Neck not dilatable, and no small maxillary teeth behind the poison-fangs.

a. Scales oblique, rostral very large and detached on the sides, subcaudals 15-45. ASPIDELAPS.

b. Scales not oblique, rostral large, subcaudals 45-50. WALTERINNESIA.

c. Scales not oblique, rostral moderate, subcaudals 20-45. ELAPS.¹

C. Maxillary bone with a strong posterior process, no solid maxillary teeth, a fang-like anterior mandibular tooth followed by a toothless space.

Head long and narrow, body slender, scales very oblique. DENDRASPIS.

II. *Asiatic Genera*

(Excluding the islands of Australasia)

A. Maxillary bone not extending forward beyond the palatine; vertebral scales enlarged. BUNGARUS.

B. Maxillary bone extending forward beyond the palatine; vertebral scales not enlarged.

1. Internasal shield bordering the nostril.

Poison-fangs followed by one or more small teeth, scales oblique, neck usually dilatable. NAJA.

¹ This genus was formerly known as *Homorelaps*, and *Elaps* used to be the name of the genus of American coral snakes now known as *Micrurus*.

2. Internasal shield not bordering the nostril.

- a. Poison-fangs followed by 1-3 solid maxillary teeth, scales not oblique, subcaudals less than 50.

HEMIBUNGARUS.

- b. No solid teeth behind poison-fangs.

- α Poison-gland not extending beyond the head.

CALLOPHIS.

- β Poison-gland extending along the anterior third of the body; heart shifted back to middle of body.

DOLIOPHIS.

III. Australian Region

(Including all the islands of the Pacific Ocean from Malay to New Guinea)

- I. Maxilla not extending forward beyond palatine; vertebral scales enlarged.

BUNGARUS.

- II. Maxilla extending forward beyond palatine; vertebral scales not enlarged.

- A. Internasal bordering the nostril; scales in 15 or more rows.

NAJA.

- B. Internasals not bordering the nostril.

1. Nasal divided; one to three small teeth in addition to the fangs.

- a. Scales in 13 or 15 rows.

HEMIBUNGARUS.

- b. Scales in 21 rows.

OXYURANUS.¹

2. Nasal entire; one or two small teeth in addition to the fangs; scales in 15 rows.

FURINA.

3. Nasal divided; no small maxillary teeth in addition to the poison-fangs.

- a. Poison-gland not extending beyond the head.

CALLOPHIS.

- b. Poison-gland extending along anterior third of the body; heart displaced to middle of body.

DOLIOPHIS.

- III. Maxilla not extending forward beyond palatine; vertebral scales not enlarged.

- A. Poison-fangs followed by seven or more small teeth, more or less distinctly grooved. Head slightly distinct from neck.

1. Pupil vertical; canthus rostralis² rounded; scales in 15 rows.

PSEUDELAUS.

2. Pupil round; canthus rostralis distinct; scales in 15 rows.

DIEMENIA.

- B. Poison-fangs followed by six or seven small teeth, more or less distinctly grooved.

1. Anterior maxillary and mandibular teeth abruptly enlarged.

- Nostril between two nasals; scales in 17 rows.

GLYPHODON.

¹ General appearance similar to that of *Pseudechis scutellatus*.

² The angle between the upper surface and the side of the snout in front of the eye. It may be distinctly angulate, or rounded off.

2. Maxillary and mandibular teeth gradually decreasing in size.

Nostril between first upper labial, two small nasals, and the internasal; scales in 17 rows.

OGMODON.

- C. Poison-fangs followed by one to six small teeth, which may be indistinctly grooved.

1. Head not distinct from neck; habit elapiform.

- a. Eye with a vertically elliptic pupil, præocular present.

* Nostril in a single nasal.

RHYNCHELAPS.

** Nostril between two nasals.

APISTOCALAMUS.

- b. Eye with a round pupil.

* Nostril in a single nasal.

† No præocular; no internasals; scales in 13 rows.

ULTROCALAMUS.

†† Præocular present; scales in 15 rows.

PSEUDAPISTOCALAMUS.

** Nostril between two nasals; scales in 15 or 17 rows.

TOXICOCALAMUS.

2. Head more or less distinct from neck; habit colubriiform.

- a. Internasals distinct; rostral moderate.

* Scales not oblique; smooth.

† Ventrals rounded.

‡ Eye rather small; canthus rostralis distinct; subcaudals all or partly in two rows.

PSEUDECHIS.

‡‡ Eye rather small; canthus rostralis rather indistinct; subcaudals (with one exception) single.

DENISONIA.

‡‡‡ Eye very small; tail short; subcaudals in two rows.

MICROPECHIS.

†† Ventrals angulate and notched laterally, subcaudals single.

HOPLOCEPHALUS.

** Scales not oblique, strongly keeled; subcaudals single.

TROPIDECHIS.

*** Scales oblique and smooth, dorsals longer than laterals; subcaudals single.

NOTECHIS.

- b. Internasals absent; rostral extremely large; subcaudals single.

RHINHOPECEPHALUS.

3. Head very distinct from neck. Habit viperiform.

a. Scales smooth: subcaudals single. BRACHYASPIS.

b. Scales more or less distinctly keeled; subcaudals anteriorly single, posteriorly paired; tail compressed at the end and terminating in a long spine. ACANTHOPHIS.

D. No maxillary teeth except the poison-fangs; nasal entire; subcaudals single. ELAPOGNATHUS.

IV. American Region.

(A single genus of about 30 species)

A. Head not distinct from neck; tail short; eye very small. MICRURUS.¹

The "Coral Snakes" are usually annulated in black, red, and yellow. Many harmless Colubrids are similarly marked, but *Micrurus* may be distinguished as such by the absence of loreal shield, and by the poison-fangs, which are not followed by any other maxillary teeth.

VIPERIDÆ

The family Viperidæ is also divided into two subfamilies—(1) the Vipers, and (2) the Pit-Vipers, all of which are very dangerous. The skull has distinctive characters, the most important of which is the movable facial bones.

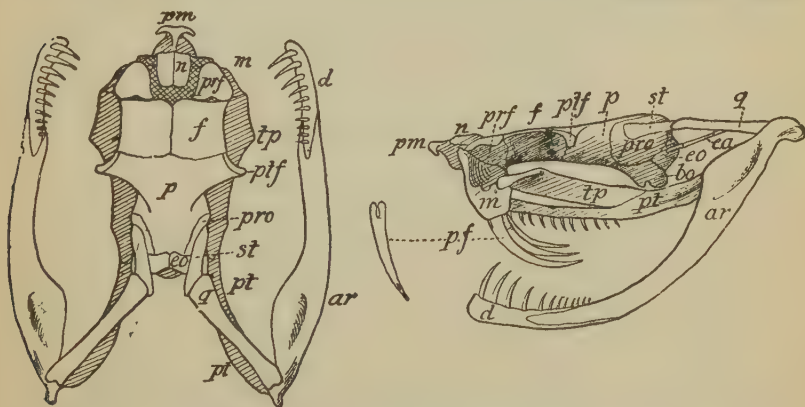


Fig. 380.—Skull of *Trimeresurus gramineus*, upper view and side view. (After Boulenger, "A Vertebrate Fauna of the Malay Peninsula: Reptilia and Batrachia.")

ar, Articular; bo, basioccipital; ca, columella auris; d, dentary; eo, exoccipital; f, frontal; m, maxillary; n, nasal; p, parietal; pf, poison-fang; pm, pramaxillary; prf, prefrontal; pro, prootic; pt, pterygoid; pif, postfrontal; q, quadrate; st, supratemporal; tp, transpalatine.

The vertically-erectile maxillæ operate the fangs, which are enormously enlarged, strongly curved, tubular, and are thus also vertically erectile. When out of action the fangs and accessory fangs are laid back against the roof of the mouth, as they are too long to allow the mouth to shut when erected. (Fig. 380.)

¹ Formerly *Elaps*.

The two subfamilies are defined as follows :—

- | | |
|-------------------------------|-------------------------|
| I. A loreal pit. ¹ | CROTALINÆ (Pit-Vipers). |
| II. No loreal pit. | VIPERINÆ (Vipers). |

The loreal pit is a deep sensory pit situated behind or below the nostril, but in front of the eye.

VIPERINÆ

These Vipers are usually called the Old World or True Vipers, as distinct from the Crotalines. They do not occur at all in America or in the Australian region, and are most numerous in Africa, where many large and deadly species occur. The most dangerous ones are the Puff-Adders (*Bitis spp.*) of Africa and Russell's Viper (*Vipera russelli*) in India.

SYNOPSIS OF VIPERINÆ

I. African Genera

- | | |
|---|--------------|
| A. Some or all of the head-shields broken up into small shields or scales. Habit viperiform. | |
| 1. Lateral scales as large as dorsals, without serrated keels. | |
| a. Nasal separated from the rostral by small scales; supranasal present, crescentic. | BITIS. |
| b. Nasal in contact with rostral, or separated by a naso-rostral shield. | VIPERA. |
| 2. Lateral scales smaller than dorsals, slightly oblique, keels not serrated; tail prehensile; subcaudals single. | ATHERIS. |
| 3. Lateral scales smaller than dorsals, obliquely set, with serrated keels. | |
| a. Ventrals laterally angulate, subcaudals in two rows. | CERASTES. |
| b. Ventrals rounded, subcaudals single. | ECHIS. |
| B. Head covered with large symmetrical shields as in the Colubridæ. Habit colubriiform. | |
| 1. Mandibular teeth well developed; eye moderate. | CAUSUS. |
| 2. Mandibular teeth reduced to two or three in middle of dentary; eye minute. | ATRACTASPIS. |

II. European and Asiatic Genera

- A. Head-shields broken up into small shields or scales.

¹ Hence the name of Pit-Viper.

1. Lateral scales as large as dorsals, without serrated keels.
 - a. Nasal in contact with rostral, or separated by a naso-rostral shield. VIPERA.
 - b. Nasal separated from rostral by small scales. PSEUDOCERASTES.
2. Lateral scales smaller than dorsals, oblique, with serrated keels.
 - a. Ventrals laterally angulate; subcaudals in two rows. CERASTES.
 - b. Ventrals rounded; subcaudals single. ECHIS.

CROTALINÆ

The Crotalines or Pit-Vipers replace the True Vipers in both North and South America, where they are more deadly than any other snakes. Well-known examples are the Bushmaster, Fer-de-lance, Moccasin, and Copperhead.

Two genera crop up in south-eastern Asia and the Indo-Australian archipelagos, in the islands of which they are the only representatives of the family Viperidæ. They are not found in Australia itself.

A second large group are the Rattlesnakes, all inhabitants of America. The "rattle" is composed of loosely jointed segments of horn, and is operated by violent caudal vibrations.

SYNOPSIS OF CROTALINÆ

(Recognized by the loreal pit)

I. Indo-Australasian Genera

- A. Upper surface of head covered with large symmetrical shields, the internasals and præfrontals sometimes broken up into scales. ANKISTRODON.
- B. Upper surface of head covered with scales or small broken-up shields. (Fig. 380.) TRIMERESURUS.

II. American Genera

- A. No rattle.
 1. Head covered with large symmetrical shields, etc. ANKISTRODON.
 2. Head covered with scales.
 - a. Posterior subcaudals replaced by small scales. LACHESIS.
 - b. Subcaudals normal; single or in pairs. TRIMERESURUS.
- B. Tail ending in a rattle.
 1. Head covered with nine symmetrical shields. SISTURUS.
 2. Head covered with scales or small shields. CROTALUS.

A Short Bibliography of Useful Works

- Boulenger, G. A.**, Catalogue of Snakes in the British Museum, Vol. III. Brit. Mus. N.H., 1895.
1. "A List of the Snakes of the Belgian and Portuguese Congo, Northern Rhodesia and Angola," *Proc. Zool. Soc.*, London, 1915, p. 193.
 2. "A List of the Snakes of Madagascar, Comoro, Mascarenes, and Seychelles," *l.c.*, p. 369.
 3. "A List of the Snakes of East Africa, North of the Zambesi and South of the Soudan and Somaliland, and of Nyasaland," *l.c.*, p. 611.
 4. "A List of the Snakes of North-East Africa, from the Tropic to the Soudan and Somaliland, including Socotra," *l.c.*, p. 641.
 5. "A List of the Snakes of West Africa, from Mauritania to the French Congo," *l.c.*, 1919, p. 267.
 6. "A List of the Snakes of North Africa," *l.c.*, p. 299.
- "Fauna of British India" (Blanford): Reptilia and Batrachia. 1890.
 "Fauna of the Malay Peninsula: Reptilia and Batrachia." 1912.
 "Snakes of Europe." London, 1913.
- Blanford**, "Eastern Persia." Vol. II, Zoology and Geology. London, 1876.
- Brazil**, "Défense contre l'Ophidisme," 2nd Ed. São Paulo, 1914.
- Calmette**, "Les Venins, des Animaux venimeux, et la Sérothérapie," 2nd Ed. Paris, 1907.
- Ditmars**, "Reptile Book." New York, 1920.
- FitzSimons**, "Snakes of South Africa." Capetown, 1912.
- Gadow**, "Amphibia and Reptiles." Cambridge Natural History, Vol. VIII.
- Jan**, "Iconographie générale des Ophidiens." Milan, 1860-66.
- Kreft**, "The Snakes of Australia." Sydney, 1896.
- Phisalix**, "Venin." Vols. I and II. Paris, 1922.
- Pratt**, "Manual of the Vertebrates of the United States." York, Pa., U.S.A., 1923.
- Rooij**, "Indo-Australasian Reptiles." Vol. II, Ophidia. Leyden, 1917.
- Smith, M.A.**, "Sea-Snakes," Brit. Mus. N.H., 1926.
- Stejneger**, "Herpetology of Japan and Adjacent Territory." Bulletin 58, Smithsonian Inst., U.S. Nation. Mus., Washington, 1907.
- Wall**, "The Poisonous Terrestrial Snakes of our British Indian Dominions (including Ceylon). and how to Recognize them; with Symptoms of Snake Poisoning and Treatment." Bombay Nat. Hist. Soc., 1913.
- "The Snakes of Ceylon." Colombo, 1921.
- "How to Identify the Snakes of India." Karachi, 1923.

Section B.—LABORATORY METHODS

I.—CLEANING SLIDES AND COVER-SLIPS

NEW slides are suitable for making blood-films, directly the superficial grease is removed, by breathing on them and rubbing up with a clean handkerchief.

Slides which are dirty or have previously been used should be boiled in a soapy solution for about half-an-hour, then washed in several changes of water, and finally polished with old linen dipped in methylated spirit.

For finer work, dirty slides or cover-slips are boiled for half-an-hour in a mixture of—

Concentrated sulphuric acid	.	.	.	6 parts
Potassium bichromate	.	.	.	6 „
Water	.	.	.	100 „

They are then thoroughly washed in water, transferred to spirit, and dried as required.

Cover-slips and slides are apt to become frosted when kept long in the tropics; in order to prevent this they should be kept in spirit.

II.—METHODS OF PREPARATION OF BLOOD-FILMS

THIN FILMS

Take on the end of a slide a droplet of blood, obtained by pricking the cleansed finger or ear-lobe¹; if possible, no pressure should be exerted, and care should be taken not to touch the skin. A second slide should be touched, about $\frac{3}{4}$ in. from the end, with the drop, and the blood allowed to run along the edge. The spreading slide should be pushed, at an angle of 45° , to the opposite end of the horizontal, leaving a thin and evenly-spread film which should be allowed to dry. (Fig. 381.) An angle of less than 45° makes a thinner, and one greater than this angle a thicker, film. (Fig. 382.)

A lancet-pointed hare-lip pin makes a very satisfactory instrument for pricking the finger. If such a pin be not handy, a good supply of blood can be obtained by means of a glass needle which is made by drawing out a Widal tube and knocking off the point an inch from the pointed end.

Films for making a differential count of cells should be prepared by pressing unevenly upon the slide, so as to obtain a wave-like film. By this means the leucocytes collect along the edges of the waves, enabling the enumeration to be done more rapidly.

THICK FILMS

Ross's thick film is made by allowing some six drops of blood to fall on a slide within an area 5–7 mm. in diameter, and spreading them into an even layer. After de hæmoglobinization with water the resulting film is

¹ See p. 861. Blood from the ear is not so satisfactory as that obtained from the finger.

dried in air. The film should then be stained with Leishman's or Giemsa's stain, as detailed at p. 859.

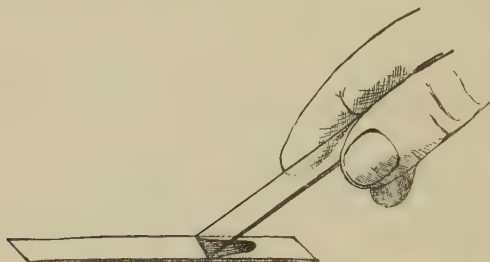


Fig. 381.—Method of spreading a blood-film.

There is considerable difficulty in differentiating the younger forms of benign tertian and quartan from subtertian malaria parasites by this

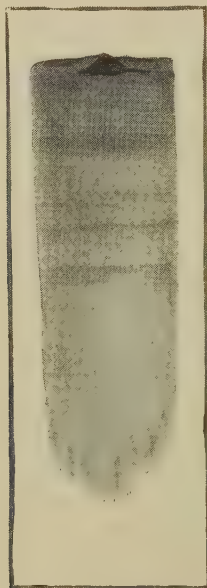


Fig. 382.—Successful thin blood-film. (*Orig.*)

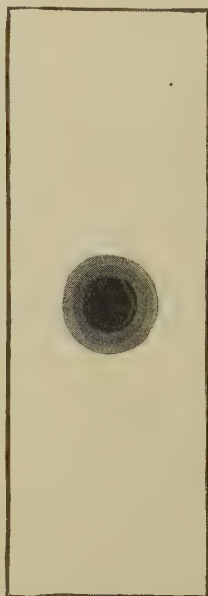


Fig. 383.—Thick blood-film. (*Orig.*)

method, such details as Schüffner's dots being rendered invisible. It is, however, very useful for demonstrating parasites in scanty infections, especially in the case of the gametocytes of benign tertian and the crescents of subtertian, and it is also useful for the demonstration of the spirochaetes of relapsing fever and trypanosomes when these, as is often the case, are extremely scanty (*see* Plate VII, 1, facing p. 40).

Films for demonstration of filarial embryos.—An even larger-sized drop should be taken (20 c.mm.) and spread so as to occupy an area of $\frac{1}{2}$ sq. in. on the slide. (Fig. 383.) For this purpose the finger should be pricked with a broad-pointed needle and the surface dabbed with four good-sized drops. The film is allowed to dry, protected from dust (especially cotton fibres, which may simulate microfilariae), dehaemoglobinized, and stained at the same time in a dilute watery solution of fuchsin (5 drops to 150 c.c. distilled water), then examined in a wet state under a low power of the microscope.

PREPARATIONS FOR THE STUDY OF FRESH BLOOD

A small drop of blood should be taken upon a clean slide, inverted, and allowed to come into contact with a clean cover-slip upon a filter-paper. If no pressure is used, the blood spreads out evenly, the corpuscles tending to congregate round the periphery while the centre remains clear. The preparation may then be ringed with vaselin, and the blood-cells or contained parasites studied in the living state under a $\frac{1}{2}$ -in. lens. Should it be desired to study the action of living cells (vital staining), a vaselin ring or square of the size of a cover-slip is made upon a clean slide. Then a solution of 0.85-per-cent. NaCl with 1-per-cent. sodium citrate is tinted with methylene-azur, gentian-violet, or methyl-green, and taken up in a capillary pipette, together with an equal volume of blood. After mixing quickly on a slide, a small drop is placed in the centre of the vaselin ring and immediately covered with a cover-slip and pressed down.

III.—STAINING OF BLOOD-FILMS FOR PROTOZOA AND FOR THE DIFFERENTIAL COUNT OF CELLS

Leishman's method.—For this method *no preliminary fixation* is required.

Preparation of stain from the powder—0.15-per-cent. solution dissolved in methyl-alcohol (acetone-free). The powder is placed in a glass mortar, a quantity of methyl-alcohol added, and the powder ground down with a pestle until the alcohol is saturated. The fluid is now decanted off into a clean bottle and a further fraction of methyl-alcohol added to the residue in the mortar, which is again ground down until as much as possible is dissolved. This process is repeated until the whole of the powder is in solution, and sufficient methyl-alcohol is added finally to the stain to make up the required volume.

Method of staining.—1. Select the most suitable part of the blood-film and place a grease-pencil mark on each side, about 1 in. apart—a method which in staining large batches of films results in great economy. 2. Cover the selected part with stain by means of a pipette, and leave for a minute, taking care that it does not dry. 3. Dilute the stain about 1 in 4 with distilled water, *which must not be acid in reaction* (fresh rain-water may be used), and allow to act for a further 5 mins. (See Tribondeau's test, p. 861.) 4. Wash off the stain with distilled water and leave a drop on for a minute to differentiate; place in a sloping position to drain. (Fig. 383.)

For permanent preparations, Leishman-stained slides must *not* be mounted in Canada balsam, as they rapidly fade, unless it is neutral in reaction, or dammar lac be used; they should be examined, unmounted, direct in cedar-wood oil, and the oil subsequently removed by means of xylol.

Giemsa's stain.—It is best to obtain the stain already prepared for use by Grüber. *The film must first be fixed* by placing in a mixture of equal parts of absolute alcohol and ether for 10–15 mins.

Method of staining.—1. The film should be covered with a 1 : 20 dilution of the stain (1 drop to 19 drops distilled water), which is allowed to act for 20-30 mins. 2. Wash off the stain with distilled water; place the slide in a sloping position to drain, or dry with blotting-paper.

Hæmatoxylin and eosin.—For studying the finer structure of the leucocytes, and especially the nuclear changes, blood-films should be stained with hæmatoxylin and eosin.

After fixation in alcohol and ether for 10 mins. the film should be stained with Delafield's hæmatoxylin for 7 mins. The stain should be well flushed off the film with a good flow of tap-water, and it should be left in a running stream of the same for an equal period in order to "blue" thoroughly. While still wet it should be counterstained with a watery solution (5-per-cent.) of eosin for 30 secs., after which it should be thoroughly rinsed in tap-water for another 3 mins. in order to differentiate the eosin.

Method of staining the flagellated body in malaria.—A sheet of thick blotting-paper, having rows of oblong holes (1 in. by $\frac{3}{8}$ in.) cut in it, is prepared; it is slightly but sufficiently moistened with water, and laid smoothly on a sheet of window-glass.

A patient in whose blood the gametocyte form of the parasite abounds is selected. A clean microscope slide is breathed on once, and the droplet of gametocyte-containing blood immediately taken up by lightly touching it with the centre of the breathed-on surface of the slide. The blood is now rapidly and somewhat unevenly spread out with the needle so as to cover an area of about $\frac{3}{4}$ in. by $\frac{1}{2}$ in. The slide is immediately inverted over one of the blotting-paper cells and pressed down sufficiently to secure thorough apposition of the slip to the paper, without, at the same time, bringing the blood into contact either with the moistened paper forming the wall, or with the glass forming the floor of what is now a very perfect moist chamber. The rest of the paper cells are rapidly covered with blood-charged slides prepared in the same way. Slides are removed and dried at intervals of from five to twenty minutes and are subsequently stained by Leishman's method.

McKay's method.—This is an abbreviated but more effective method. A thin film of crescent-containing blood is made upon a thin slide (1 mm. in thickness, so as to be easily focused through

a $\frac{1}{8}$ -in. lens). The wet film should be breathed upon and then placed face downwards upon a second slide covered with a small piece of damp filter-paper, in the centre of which a small opening is cut. The two slides are bound together by means of elastic bands, thus forming a tightly sealed damp chamber. The exflagellation of the crescent can now be observed under the microscope, and immediately this occurs the film is dried and stained in the ordinary manner. (See Fig. 384.)

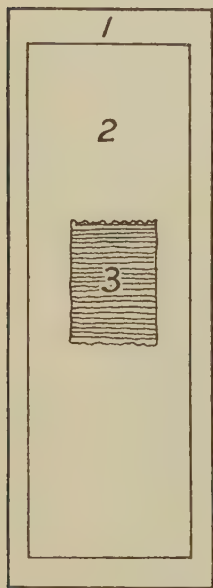


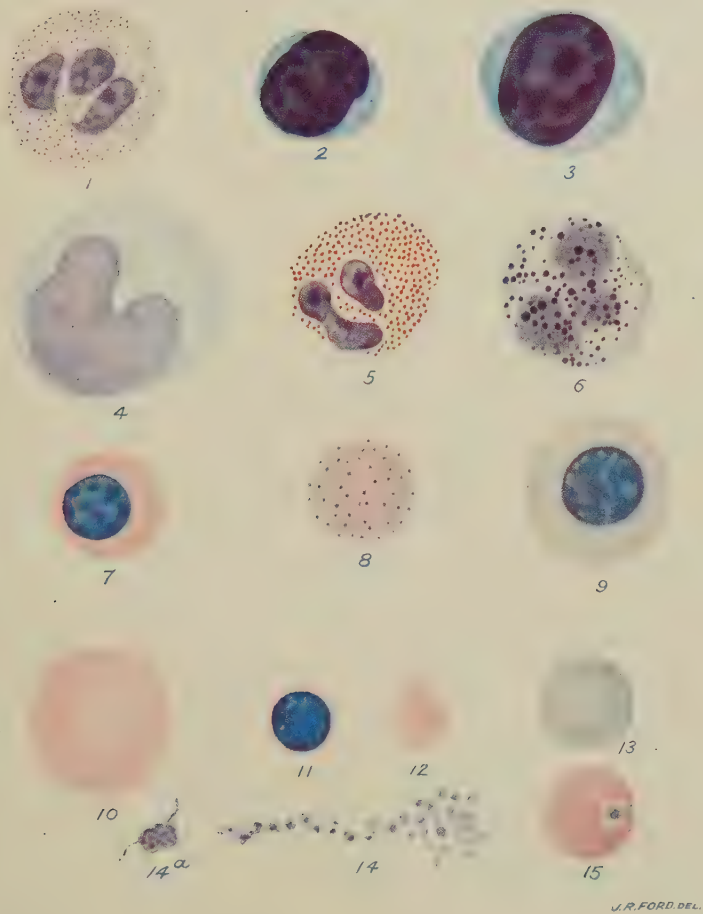
Fig. 384.—To illustrate McKay's method of staining flagellated body.

1, Slide bearing freshly-made blood-film; 2, pad of damp filter-paper; 3, size of opening showing blood-film and forming with the opposing slide an hermetically sealed damp chamber.

PLATE XXXIV

NORMAL AND ABNORMAL BLOOD-CELLS.

- 1.—Neutrophile polymorphonuclear leucocyte.
- 2.—Small lymphocyte.
- 3.—Large lymphocyte.
- 4.—Hyaline or large mononuclear leucocyte.
- 5.—Eosinophile leucocyte.
- 6.—Basophile leucocyte ("mast-cell").
- 7.—Normoblast (nucleated red cell).
- 8.—Basophilic dots in red cell.
- 9.—Megaloblast.
- 10.—Megalocyte.
- 11.—Microblast.
- 12.—Microcyte showing poikilocytosis.
- 13.—Polychromatophilic degeneration of red cell.
- 14, 14a.—Various appearances of blood-platelets.
- 15.—Blood platelet superimposed upon a red cell.



NORMAL AND ABNORMAL BLOOD-CELLS.

× 2,000. (Leishman's stain.)

PLATE XXXIV

Tribondeau's hæmatoxylin test for reaction of distilled water.—Two drops of a saturated alcoholic solution of hæmatoxylin should be added to a test-tube half-filled with the water under examination. If the water be neutral, the purple colour of hæmatoxylin will develop in 2–4 mins.; if alkaline, the colour develops immediately; if acid, it is delayed.

IV.—VARIETIES OF BLOOD-CELLS, AND THEIR SIGNIFICANCE (Plate XXXIV)

The average total leucocyte-count, as performed on a Thoma-Zeiss hæmocytometer, is 7,000 per c.mm. of blood. A rise to above 10,000 indicates a *leucocytosis*, a fall to below 5,000 a *leucopenia*. In making a differential leucocyte-count, at least 300 cells should be counted under the $\frac{1}{2}$ -in. immersion lens, and by means of a movable stage the preparation should be moved from side to side, so as not to traverse the same field twice. In a "wave" preparation the edge of the thickened portions will be found to contain the majority of the leucocytes; a knowledge of this fact will save considerable search.

The neutrophile polymorphonuclear (or microphage).—Normal proportion, 60–70 per cent.; average, 67. Increased in liver abscess, pneumonia, relapsing fever, and in any septic process. Size when spherical, 10 μ . In liver abscess the polymorphonuclear leucocytosis is not usually considerable, unless the pus is under pressure.

Lymphocyte.—Normal proportion, 19–30 per cent.; average, 23. The small lymphocyte is 5–8 μ in diameter, the large lymphocyte 8–10 μ . This cell is increased after physiological digestion and in undulant fever, pellagra, enteric, and relatively so in kala-azar.

Large hyaline, or mononuclear (or macrophage, including so-called transitional).—Size, 14–21 μ . Normal proportion, 3–8 per cent.; average, 6 per cent. This cell is increased in all protozoal diseases, trypanosomiasis, leishmaniasis, and malaria; in the latter it often contains ingested hæmoglobin. In making an estimate of the proportion of mononuclear cells in a film, not less than 300 leucocytes should be counted. Should the ear be selected for obtaining blood, it is important that no drop earlier than the third should be used, for it has been shown that the mononuclears tend to accumulate in the capillaries of the ear if the local circulation is slow. It is now known that the large mononuclears are derived from the myelocyte group, and are not related to the lymphoid cells, therefore the so-called transitional cells must be regarded as mononuclears.

A proportion of 15 per cent. or over of these cells may be considered a reliable aid to the diagnosis of malaria; a proportion of 10 per cent. occurs in a normal person, and a percentage above this calls for further investigation. There is no increase of mononuclears during the pyrexia of a malarial attack, but an increase may take place during the apyretic period (see p. 58).

Eosinophile.—These cells are a little larger than the polymorphonuclear leucocyte—12–14 μ . Normal proportion, 2–4 per cent.; average, 3 per cent. Eosinophiles are increased in all helminthic diseases—in ancylostome, dracunculosis, and clonorchis infections, 5–10 per cent.; in filariasis and paragonimiasis, 10–20 per cent.; and in schistosomiasis and trichinosis, 20–60 per cent. of the total leucocyte-count. In ascaris and dibothriocephalus infections there may be little or no increase.

Basophile.—Slightly smaller than the polymorphonuclear—9 μ in diameter. Usual proportion, 0.5 per cent.

Leucocytes in childhood.—The leucocytes are more numerous in the child than in the adult; 12,000 per c.mm. is the average number throughout infancy. The percentage of lymphocytes is doubled, that of the neutrophils is halved. The adult proportion, as given above, is reached about the tenth year.

Normal red cell (erythrocyte).—Size, 7.2–7.5 μ in diameter. Normal number, 5,000,000 per c.mm., or a little over. They are biconcave discs, and therefore considerably thinner in the centre than at the periphery. A total red count, computed from 64 squares on the Thoma-Zeiss hæmocytometer, of under 3,000,000 denotes a severe anæmia, and is usually accompanied by degenerative changes in the red cells—e.g. malaria, blackwater fever, sprue, ancylostomiasis, Oroya fever.

A distinctive form of red cell—the *reticulocyte*—has recently been described. They constitute a constant sign of blood-regeneration, and may be stained by cresyl-blue which is used for the blood-count. The stroma of the cells contains a blue-staining reticulum. In normal blood these cells amount to one per cent., but during blood-regeneration they may reach 20 per cent.

Anisocytosis denotes an inequality of size of red cells; it is found in various conditions of anæmia, especially of the pernicious type. **Poikilocytosis** denotes various shapes of cells, giving the idea of fragmented corpuscles such as are found in anæmic conditions.

Megalocyte.—A red cell of abnormal size and shape, generally associated with microcytes—i.e. small red cells one-quarter to one-half the size of the normal. Megalocytes are indicative of degenerative changes of the blood in the severe anæmias of blackwater fever, subtertian malaria, Oroya fever, and pernicious anæmia.

Nucleated red cell, or erythroblast.—Present in very small numbers in normal blood, increased in severe plastic anæmias—e.g. malarial cachexia, blackwater fever, sprue, ancylostomiasis, kala-azar, and Oroya fever—and in severe helminthiasis. The nucleus is sometimes double or bilobed, and the protoplasm of the cell is usually polychromatophilic. These cells are generally present in considerable numbers in spleen punctures in kala-azar, severe malaria, Egyptian splenomegaly, pernicious anæmia, and Banti's disease.

Polychromatic degeneration of red cells.—Present in subtertian malaria, blackwater fever, and severe anæmia. The term *polychromasia* denotes a degeneration of the red cell, the cytoplasm of which stains light blue; when severe it is generally accompanied by the formation of polychromatic, or basophilic, dots. It is indicative of some toxic absorption, and not pathognomonic of any special disease, for it is found in malaria, verruga peruana, pernicious anæmia, ancylostomiasis, and lead-poisoning.

Megaloblast.—Size, two to four times that of a red corpuscle. It is an abnormal nucleated red cell found in severe anæmias of the pernicious type, including dibothriocephalus infections. Its presence in the blood generally indicates a regeneration from the blood-forming cells in the bone-marrow.

Blood-platelets.—Size about 3 μ in diameter, round, oval, or rod-shaped, according to the viewpoint. When resting on red cells they may simulate malaria parasites, but there is always a clear zone due to pressure surrounding the platelet. (Plate XXXIV, Fig. 15.) When drawn out in making

the film they may simulate a trypanosome. They are generally found in masses or in strings, are coated with some adhesive substance, and cling to any stationary object. Their function is connected with the clotting of the blood.

V.—ENUMERATION OF BLOOD-CELLS AND ESTIMATION OF HÆMOGLOBIN

1. ENUMERATION OF RED BLOOD-CORPUSCLES BY THE THOMA-ZEISS HÆMOCYTOMETER

This instrument consists of a graduated mixing pipette and a counting-slide. The blood is obtained by pricking the finger. It is advisable to give a sharp stab, in order to make such a wound that the blood flows freely, so that no squeezing is necessary. The blood is then sucked up to the 0·5 mark on the graduated red pipette, every care being taken not to pass this point. The excess of blood at the end of the pipette should be removed by wiping with a clean cloth. Without delay the blood should be diluted as far as the 101 mark on the pipette with 2-per-cent. sodium citrate in 0·85-per-cent. sodium chloride. Filter before use.

The pipette should then be taken between the thumb and forefinger and shaken vigorously for one minute so that the blood and diluting fluid become well intermingled. The blood is now in a dilution of 1:200. The small amount of fluid remaining in the capillary tube is blown out, while the remainder is transferred to a clean watch-glass.

The blood, diluted in this manner, is placed on the counting-slide as follows: The circular platform of the slide is almost covered with a cover-glass, and some of the diluted blood in a capillary pipette is run underneath the free margin. In this manner just sufficient fluid is injected to obtain the correct depth of 0·1 mm. for counting purposes.

The blood-cells are permitted to settle for about 3 mins., and the preparation is examined under the low power to ascertain their proper distribution, absence of air-bubbles, and foreign bodies. At least four sets of 16 small squares each should be counted with the $\frac{1}{4}$ -in. objective, and the figure obtained, multiplied by 12,500, will speedily give the total number of red blood-corpuscles per 1 c.mm. of fluid blood.

2. ENUMERATION OF WHITE CELLS BY THE THOMA-ZEISS HÆMOCYTOMETER

A special pipette of a larger bore is supplied for this purpose and permits of a smaller dilution of the blood. The diluting fluid is a 1-per-cent. solution of glacial acetic acid in distilled water. The blood is sucked up to the 0·5 mark, the fluid to mark 11, resulting in a 1:20 dilution. Once the pipette is filled, it should be placed in a horizontal position, as the fluid is very apt to escape. After shaking, the fluid is transferred to the counting-slide as already described, and the cells are allowed to settle for 3 mins. The whole of the 16 larger squares should be counted and the figure obtained multiplied by 312, which will give the total number of leucocytes in 1 c.mm. of blood.

3. ESTIMATION OF HÆMOGLOBIN

The method of estimating hæmoglobin by means of Gower's hæmoglobinometer is the one to be recommended for general use in the tropics. A few drops of distilled water should be placed in the graduated tube supplied with the instrument. A small quantity of blood is drawn up to the graduation

mark on the special pipette, and any excess is wiped away from the end. The blood is now transferred to the distilled water in the graduated tube, and by mixing and adding water, drop by drop, the tint is made to match that of the standard colour tube. The level at which the mixture stands in the graduated tube is now read off. If this be at (say) 60, then the blood contains 60 per cent. of hæmoglobin.

A practical method of hæmoglobin estimation for everyday use is that of Tallqvist, in which the colour of the blood on blotting-paper is compared with a standard colour-scale.

The simplest method of estimating the "colour index," that is the relative amount of hæmoglobin in terms of that contained in each corpuscle, is obtained by the formula $CI = \frac{H}{2E}$; then H stands for hæmoglobin percentage and E for the first two figures of the erythrocyte-count (if in millions).

VI. PREPARATION OF SPECIAL CULTURE MEDIA

Nicolle, Novy, and MacNeal medium (N.N.N.), for cultivation of leishmania and other protozoa.—*Composition* :

Agar	14	gram.
Sodium chloride	6	"
Water	900	c.c.

The agar and the sodium chloride are added to the water in a flask, well shaken, and dissolved by steaming for two hours. The hot solution is then filtered through cotton-wool, and about 3 c.c. are afterwards distributed into each of 50 test-tubes and sterilized in the autoclave at 120° C. for 20 mins.

The medium is cooled to 55° C., and into each tube are dropped 20 drops of whole rabbit's blood as described in connexion with the Noguchi-Wenyon medium (*see below*).

The tubes are "rolled" in the hand and "sloped" upon a glass rod. When the agar has set, they are incubated for 24 hours to test for sterility and to allow them to "sweat." They are now capped or sealed with paraffin wax. Inoculation is effected by introducing suspected material into the "water of condensation"; the tubes are kept at 22° C. and examined 5-7 days later for developmental forms of protozoa.

Adler's medium for the cultivation of *Leishmania*, etc.—Ringer's solution is placed in test-tubes in amounts of 4.5 c.c.; the tubes are placed in a waterbath and the temperature is raised to 100° C, when 0.5 c.c. of 2-per-cent. nutrient agar is added to each tube and the mixture sterilized in a Koch's steamer for one hour on three successive days. When cool, 0.5 cc. of sterile rabbit's serum is added to each tube.

Noguchi-Wenyon medium for the cultivation of spirochætes, leptospira and certain protozoa.—The medium is prepared as follows: To 270 c.c. of 0.85-per-cent. sodium chloride add 30 c.c. of ordinary 2.5-per-cent. nutrient agar pH 7.6. When thoroughly mixed, place 9 c.c. in each tube. After being autoclaved at 120° C. for half-an-hour the tubes are cooled to 55° C., and into each tube are dropped, from a rabbit's ear, 20 drops of blood. The tubes, which are not shaken, are incubated for 24 hours. The medium is then ready for use.

The blood is obtained from the rabbit by the paraffin method. The

animal is enclosed in a box at one end of which is a round aperture fitting the neck, through which the head projects. The ear is shaved over the marginal vein and is wiped over with alcoholic iodine solution. When dry, the ear is coated above, below, and on the margin with hot melted paraffin wax, so that the area of operation is covered with a thin layer through which the vein is still visible. The base of the marginal vein is clamped with a "bull-dog" clip, with a sharp knife an incision is made in the vein, and the sterile blood is allowed to drop from the paraffined margin of the ear into the tubes. After incubation of the blood-agar tubes it will often be found that the blood has coagulated in a cylindrical column, leaving a clear agar medium around it.

In this medium *Leptospira icterohæmorrhagiæ* grows readily, and subculture requires to be made once every three or four weeks.

The medium has also been employed for the culture of certain intestinal protozoa, such as *Embadomonas intestinalis*, the flagellates growing in association with numerous bacteria, but for success with the leptospira absolute sterility is essential.

Boeck and Drbohlav's medium for the cultivation of *Entamoeba histolytica*, etc.—Three whole eggs are gently beaten and poured into a clean measure with one-fourth volume of Ringer's Fluid (sodium chloride 9 gm., calcium chloride 0.24 gm., potassium chloride 0.42 gm., sodium bicarbonate 0.2 gm., distilled water 1,000 c.c.). The mixture is tubed and sloped. The tubes are placed in a slanting position in the inspissator and the temperature is gradually raised to 60° C. for one hour. After a second inspissation for a similar period on the second day, the temperature is gradually raised on the third to 80° C. for one hour.

A second solution is made as follows: To 1,000 c.c. of Ringer's Fluid the whipped white of one egg is added; the liquid is mixed and filtered through a "candle." This is known as Locke's Solution, and the reaction should be about pH 7.6.

In order to make a culture, 5 c.c. of the Locke's solution are added to one of the egg-slants and placed in a water bath at 37° C. for a few minutes. A small portion of faces is then emulsified in the Locke's solution contained in the prepared tube and incubated at 37° C. for 24 hours.

To examine the culture, a fairly wide-bore pipette fitted with a rubber teat is obtained and a small quantity of the deposit at the bottom of the egg column removed.

Recently Brumpt has advocated the addition of a small quantity of finely-powdered rice-starch to the medium upon which the entamoebæ feed and thrive. The starch is added at the time of inoculation.

Bass's method for the cultivation of the malaria parasite—10 c.c. of aseptically drawn blood from the median basilic vein of an untreated malaria patient are immediately transferred to a large test-tube containing $\frac{1}{10}$ c.c. of a 50-per-cent. solution of Merck's dextrose. The tube is fitted with a cap through which runs a glass rod, and with this the blood is gently defibrinated. The mixture is distributed into culture-tubes so as to form columns of about 2 in., and then incubated at 40° C. After a time it settles into three layers—an upper ($\frac{1}{2}$ in.) of serum, an intermediate ($\frac{1}{10}$ to $\frac{1}{20}$ in.) of red and white corpuscles, and a bottom of red corpuscles. It is only in the red corpuscles of the very thin intermediate layer that the parasites grow and multiply. They are absent from the top layer, and die in the bottom layer. The tubes should be examined at the end of twelve hours' incubation, after which time the parasites die out. By drawing off with a fine

pipette a little of the middle layer the progress of the culture can be watched and subcultures started. To succeed with the latter, however, the leucocytes have to be removed by centrifugation. Strict asepsis and the avoidance of air-bubbles in drawing off and defibrinating the blood are indispensable. Chambelland has suggested the following modifications: The defibrinated blood is centrifugalized, the serous and leucocytic layer pipetted off and replaced with physiological saline; 0.15 c.c. of a 50-per-cent. solution of glucose is then added for 5 c.c. of original blood abstracted. Subcultures are obtained by adding one volume of the original culture, taken 1 mm. below the surface of the deposit, to five volumes of freshly-washed red blood-cells; they should be made every 48 hours.

Sinton's modification.—Sinton carries out culture of the malaria parasite in a specially constructed glass tube about 20 cm. in length, the tubing having a bore of 0.4–0.5 cm. The blood is defibrinated by means of glass beads inserted into the tube containing ascitic fluid to which 2 c.c. of a 50-per-cent. dextrose solution to every 100 c.c. has been added. Cultivation at from 35° C.–38° C. is advocated.

VII.—CULTIVATION OF ORGANISMS FROM THE BLOOD: EXAMINATION OF CEREBRO-SPINAL FLUID

Technique of culture of protozoa from splenic, hepatic puncture, etc.—In making a splenic or hepatic puncture a "Record" syringe (2 c.c.), previously dried with alcohol and ether, and fitted with a fairly large-bore platinum needle (No. 10 size, Maw), should be used. It is well to start with the plunger halfway down the barrel, so as to provide sufficient air force to expel the contents from the needle after aspiration. The portion of the spleen jutting beneath the costal margin should be selected, and puncture should be made in two stages, first through the skin, then into the substance of the spleen itself. Traction should be made upon the plunger till blood is seen in the barrel, the object being to remove as much pulp as is possible. In hepatic puncture the space between the 7th and 8th ribs, in the mid-axillary line, should be selected. The contents of the barrel should be introduced into the water of condensation of N.N.N. medium, and the tubes should be incubated for at least 10 days at 22° C. before being examined.

Lymphatic-gland puncture is practised in trypanosomiasis and leishmaniasis. The enlarged gland is held between two fingers, the skin sterilized, and the needle of the syringe inserted; and at the same time the neighbourhood of the gland is massaged. The fluid so obtained may be either cultured or made into films.

Technique of blood-culture for enteric and allied organisms.—To obtain blood from the vein, a rubber bandage, or a piece of rubber tubing, should be wound somewhat firmly round the upper arm so as to constrict the brachial vein, thus making the median basilic and cephalic prominent at the bend of the elbow. After painting the skin with a strong solution of iodine the needle of a 10-c.c. syringe should be inserted *upwards* into the most prominent vein, and traction gently made upon the piston. Directly the blood begins to flow, the rubber bandage should be loosened or removed. The blood should be allowed to flow up to the 5-c.c. mark. The needle should be then removed from the vein and detached from the nozzle. The blood should be transferred into 25-c.c. of taurocholate broth or bile. Should it be necessary to dispatch the blood specimen some distance to the nearest laboratory, sterile trypsin added in the proportion of 1 part to 20 of blood inhibits

clotting, and destroys the antibacterial properties of the blood, and thus renders successful cultivation more probable.

VENULES.—A simple and practical method of withdrawing blood for culture or for serological tests has been devised by the Behring Institute. The venule is a simple tube, or ampoule, from which air has been exhausted to form a partial vacuum. The tube has the upper rim thickened or bordered in order to grip the rubber stopper (Fig. 385, A), in which is inserted a glass capillary-tube so arranged that the bent open end impinges on the rubber and is thus hermetically sealed (Fig. 385, B). The capillary-tube is provided with a bulbous enlargement in its middle where a steel hollow needle is soldered in. By means of a file the capillary-tubing of the cannula is

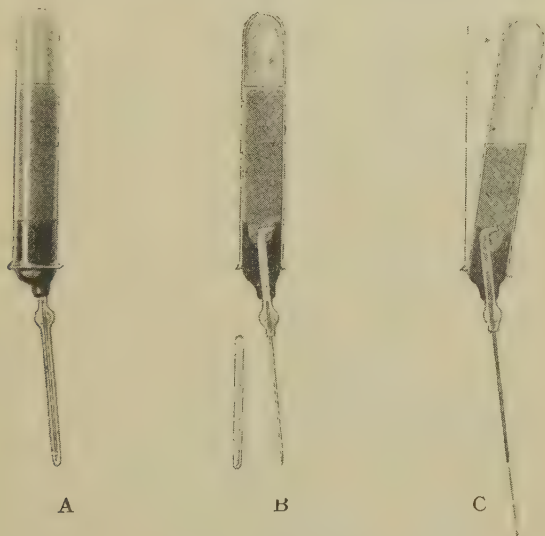


Fig. 385—Venules.

A. Venule ready for use.

B. Cross-section showing capillary-tube removed from the needle.

C. Release of the valve by pressure and filling of the tube with blood.

removed by scratching at the mark on the glass above the globular part, and broken off with gentle pressure.

Method of use.—Avoiding too great a pressure on the tube the cannula is taken at the globular part between the thumb and the index finger of the right hand and inserted into the vein, when venous blood enters the tube immediately. The cannula is now fixed with the thumb and the index finger of the left hand, and slight pressure exerted on the ampoule by means of the right, so that the joint formed by the ampoule and cannula is bent. By these means the valve (Fig. 385, c) is opened and blood is drawn up. The blood should flow in till the vessel is nearly filled, when the valve automatically closes. The ampoules are constructed so as to contain nutrient agar, bile, citrated saline, or broth, so that blood-cultures can be directly made.

For transport to a laboratory over a long distance it is recommended that

the end of the glass be warmed and closed with sealing-wax. In warm countries growth of bacteria in the blood-stream will proceed in the culture-medium during transport.

A reversal of this process can be carried out in tubes known as *serules*, where various kinds of sera, glucose solution, etc., are kept under pressure and injected into the vein in a similar manner. The *serule* contains in itself all that is necessary for an injection.

If no other means of obtaining blood is possible, the clot of blood in a Widal tube, taken from the finger with aseptic precautions, may be utilized after the serum has been abstracted for agglutination reaction.

For more delicately-growing organisms, such as the meningococcus, *Brucella melitensis* and the pneumococcus, it is advisable to use a larger quantity of medium—50 c.c. of trypsin-broth or Fildes' medium in a Florence flask containing no inhibitory constituents such as bile.

The test-tubes or flasks should be incubated for 24 hours, and a small quantity of the supernatant fluid removed by means of a sterile pipette or platinum loop and plated out on a suitable medium.

The organisms must be recognized by their biochemical and agglutination reactions. If a negative result is obtained at first, it is advisable to leave the blood-culture in the incubator for 48 hours, or, in the case of *B. melitensis*, even longer.

Examination of the cerebro-spinal fluid.—Normal cerebro-spinal fluid is clear and colourless and contains a trace of albumin, albumose, and a body (pyrocatechin) which reduces Fehling's solution. When the fluid is turbid it indicates a meningitis. The normal fluid has a specific gravity of 1010, and is under pressure of 5–7 mm. of mercury or 60–100 mm. of water; about 10 c.c. can normally be obtained. For cultural purposes the fluid should be collected in two or three test-tubes to avoid contamination of the entire sample by a drop of blood which may exude. For the Wassermann test the fluid should be taken without dilution.

In the late stages of *sleeping sickness*, trypanosomes can be demonstrated in smears obtained from the centrifugized deposit of cerebro-spinal fluid. Pleocytosis—an excess of small and large mononuclears—is noted in the cellular exudate. In doubtful cases, inoculation of the fluid into dogs or monkeys yields definite results in 10–14 days. This procedure constitutes a test of great clinical importance.

Cyto-diagnosis.—For cyto-diagnosis, 5 c.c. of cerebro-spinal fluid are centrifuged for five minutes, the supernatant fluid is poured away, the deposit spread on a slide and stained by Leishman's method.

The normal centrifuged fluid contains 2–3 lymphocytes in a microscopic field of 400 diameters. A more accurate method of counting is the Fuchs-Rosenthal modification of the Thoma-Zeiss counting apparatus; 10 c.c. of fluid are mingled in a special pipette with 1 c.c. of staining fluid containing methyl-violet and acetic acid.

An excess of cells above 10 per c.mm. is considered pathological.

VIII.—AGGLUTINATION WITH PATIENT'S SERUM FOR TYPHOID, PARATYPHOID AND UNDULANT FEVER

A simple method of macroscopic agglutination by progressive dilution of the serum in agglutination tubes can be employed, but gives only a limited range of dilution, and a considerable amount of blood (1–2 c.c.) is required. The glass capsules containing the blood should be centrifuged,

and the serum abstracted by means of a pipette. At least 5 drops of clear serum are required in order to obtain a quantity sufficient for further dilution. This amount should be mixed with 20 drops of normal saline delivered from the same pipette held in a vertical position, in order to obtain a 1 : 5 dilution. For further dilution, 20 drops of the 1 : 5 dilution are placed in the first of a row of agglutination tubes, after which 10 drops are removed and mingled with an equal amount of saline in the second tube, thus giving a dilution of 1 : 10. From these 20 drops, 10 are removed and placed in a third tube, and so on; the dilution each time being doubled. To the 10 drops of diluted serum remaining in each tube an equal amount of an opalescent emulsion of bacilli should be added, thus doubling the dilution of the suspension in which the organisms are placed. The tubes are incubated for $2\frac{1}{2}$ hours or, preferably, for a shorter period at $55^{\circ}\text{C}.$, and are then examined for agglutination against a dark background; this is generally sufficiently obvious when compared with control tubes in which bacillary emulsion diluted with saline or with normal serum has been placed. The objection to this method is the limited range of titre which it affords; in order to get a range of from 1 : 10 to 1 : 160, a row of five tubes is necessary.

In testing for typhoid and paratyphoid agglutinins, three rows of five tubes each are necessary—one for typhoid, and one each for paratyphoid A and B.

In describing the various methods, the following abbreviations are commonly used, viz. "T" for typhoid, "A" for paratyphoid A, and "B" for paratyphoid B.

A more accurate but more tedious method is **Dreyer's drop method**, for which standardized bacillary emulsions can be obtained. The standard culture is as sensitive to agglutination as is the fresh culture; it is, moreover, sterile and, if stored in a cool, dark place, can be kept indefinitely.

The highest dilution in which marked agglutination, without sedimentation, occurs and can be detected by the naked eye, is termed *standard agglutination*. When this occurs with *standard agglutinable cultures* in a serum diluted to a certain degree, then the latter figure, divided by the number given on the label of the culture employed, gives the number of *standard agglutination units* contained in 1 c.c. of the serum examined.

A stand containing 15 small agglutination tubes in three rows of five each, and two larger dilution tubes, should be taken. With a dropping pipette measure out into one large dilution tube 54 drops of normal saline solution (0.85-per-cent. sodium chloride in distilled water) by means of gentle pressure on the teat. Wash the pipette with distilled water, and subsequently with absolute alcohol and ether, so as to dry thoroughly. Take up the serum to be tested into the dried pipette. Measure out 6 drops of the serum into the dilution tube already containing the 54 drops of saline, thus obtaining a dilution of 1 : 10.

The second tube should be taken, and 3 drops of the 1 : 10 serum dilution added to 57 drops of normal saline; this gives a dilution of 1 : 200. The pipette should be carefully washed out, and to each tube in the row 15 drops of standard agglutinable emulsions of T, A, and B added. Thus:—

①	②	③	④	⑤	①	②	③	④	⑤	①	②	③	④	⑤
T					A					B				
15 drops					15 drops					15 drops				

For the addition of the diluted serum it is best to commence with the higher dilutions before proceeding to the lower ones. To tube 3 in each row

add 10 drops of 1 : 200 serum ; to tube 4 in each row add 5 drops of 1 : 200 ; to tube 1 add 10 drops of 1 : 10 dilution, and to tube 2 also add 2 drops of 1 : 10 dilution. The pipettes must be washed out before proceeding to add the saline. The addition of saline should then be made to tubes 2 and 4, which receive 8 and 5 drops respectively, while tube 5 receives no serum, but 10 drops of saline only, and acts as a control against spontaneous agglutination. This can be best represented by the following scheme :

No. of tube		Drops of normal saline				Drops of serum	
						Dilution of 1 : 10	
1	0	10
2	8	2
						Dilution of 1 : 200	
3	0	10
4	5	5
5	10	0

It will be noted that the final volume of fluid in each tube, when the bacillary emulsions are added, is 25 drops. By mathematical calculation it will be seen that in tube 1 of each row the serum acts in a dilution of 1 : 25.

In tube 2 in a dilution of 1 :	125
„ 3 „ „	1 : 500
„ 4 „ „	1 : 1,000

The tubes are examined after four hours at 37° C., or two hours at 50°–55° C., followed by 15 minutes at room-temperature. The reading is taken by comparing each tube in succession with the control tube, and is preferably made by means of artificial light against a black background. If daylight is used, the tubes should be partly shadowed by passing a finger up and down behind them.

Rapid method of macroscopic agglutination by Garrow's agglutinator (Fig. 386).—This is a practical method suitable for small laboratories, and is based upon the slide method of agglutination originally described by Broughton Alcock. It may be used for the recognition of pathogenic bacteria isolated from the blood or excreta by means of specially prepared serums. Macroscopic agglutination becomes visible in as short a period as three minutes ; no incubator is needed.

For use the following apparatus is required :

(1) A *painter's palette* (Fig. 387) for dilution of the serum. (2) A *diluting pipette* drawn from glass tubing $\frac{1}{4}$ in. in diameter and 6 in. in length. The former should deliver a drop of satisfactory dimensions (a Donald's pipette fitting Morse gauge No. 70 is the correct size)—that is, when mingled with an equal quantity of bacterial emulsion, it should not run over the edge of the glass slab. (Fig. 388.) (3) The *agglutinator slab*, a piece of plate glass $11\frac{3}{4}$ in. long by $1\frac{1}{2}$ in. wide, divided into a number of partitions by double grooves running at regular intervals of 1 cm. in order to prevent the dilutions from intermingling (Fig. 386). (4) *Set of bacterial emulsions*. The stock emulsions for use with the agglutinator for the diagnosis of enteric are *B. typhosus*, *B. paratyphosus* A, B, and C; for undulant fever, *Brucella melitensis* and *B. paramelitensis*; for bacillary dysentery, *B. Shiga* and *B. Flexner*-Y. They are made from 24-hour surface agar cultures. The growth is scraped (not washed) off the surface by means of a platinum loop and

emulsified in 0·2-per-cent. formalin in normal saline. The emulsions should be very dense, of milky consistence and uniform suspension.

In order to promote the intimate mixture of the serum under investigation and the bacterial emulsions, the slab is made to revolve by means of clock-work at a uniform rate of about 15 revolutions per minute. For field use the slab may be placed in a simple box provided with damp blotting-paper in order to obviate desiccation, and turned by hand with an iron handle attached to a wooden shaft which supports the glass slab.

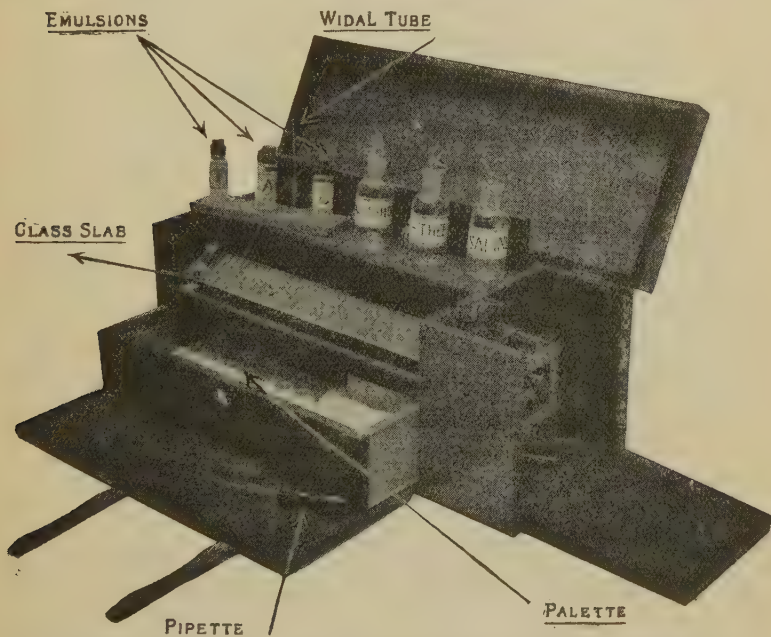


Fig. 386.—Garrow's agglutinator, for rapid macroscopic agglutination.¹

The diluting process.—The blood for examination is taken from the finger and collected in a capsule. Three large drops of blood are sufficient; the ends of the tube are sealed with wax or plasticine. (Fig. 389.) After standing for some time the serum separates, rendering centrifugalization unnecessary. By means of the pipette, 2 drops of clear serum are abstracted and placed in the first partition of the mixing palette. In order to make a dilution of 1:5, 8 similar drops of normal saline are added. From the resulting 10 drops of diluted serum, 5 are then placed in the next partition and a similar amount of saline added; and so on, thus making a series of dilutions from 1:5 to 1:80 or higher. It is important that the pipette be held vertically throughout the process, to ensure equality in size of the drops.

¹ This instrument can be obtained from Messrs. Baird & Tatlock, Ltd., Cross Street, Hatton Garden, London, E.C.1.

The mixing process.—The process of mixing the blood-serum and bacterial emulsion is carried out on the agglutinator slab. It is essential that the slab be perfectly free from grease, or the drops will not run together. It should be cleaned after each test by (1) washing in 1 : 20 carbolic acid, (2) cleansing with alcohol, and (3) drying with ether. It is a good plan to keep a piece of

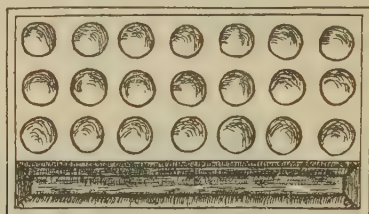


Fig. 387.—Palette for diluting serum.

old linen specially for this purpose. In cold weather the drops can be made to run more freely by gently heating the slab before use, or by breathing on the slab before the drops of bacillary emulsion and serum dilutions intermingle.

Holding the pipette vertically, begin with the highest dilution, and deposit drops of the various dilutions of serum in triplicate (if, for example, agglutination against T, A, and B is being carried out) on the slide. Opposite each drop of serum place a drop of bacterial emulsion, sterilizing the pipette



Fig. 388.—Pipette for use with agglutinator, showing method of protecting the point. One-third nat. size.

by drawing into and expressing from it (1) alcohol, (2) ether, between each emulsion.

Fig. 390 shows the appearance of the slab after carrying out the above process.

The slide so prepared is placed in the moist chamber of the mechanical mixer, where it is held fast by means of a clip at each end of the shaft. The clockwork is put into operation and the slide is allowed to revolve slowly for 3 mins. The result is that the drops of diluted serum run into and mix



Fig. 389.—Type of tube for collecting blood. Nat. size.

freely with the corresponding equal drops of bacterial emulsion, producing mixtures having serum titres of 1 : 10, 1 : 20, 1 : 40, and so on. (Fig. 391.)

At each complete revolution of the slide the bulk of these mixtures runs to and fro across the slide. At the end of 3 mins. the clockwork is stopped and the slide removed, and examined by the naked eye (if necessary, by a pocket lens) in a good light against a dark background. Agglutination converts the mixtures from homogeneous milky emulsions into a condition in which the agglutinated masses of bacilli float about like minute flakes

in a clear fluid. In a strongly agglutinating serum this takes place almost instantaneously after the agglutinator slab begins to revolve. In higher dilutions the change may take 3-4 mins., and be observable only with the aid of a pocket lens. If no change is visible with the pocket lens in the 1:10 dilution at the end of 5 mins., no agglutination of any diagnostic significance is present in the blood.

Fig. 392 shows the appearance of the agglutinator slide in the case of a patient whose blood agglutinates T up to 1:320, B up to 1:160, the A emulsion being negative.

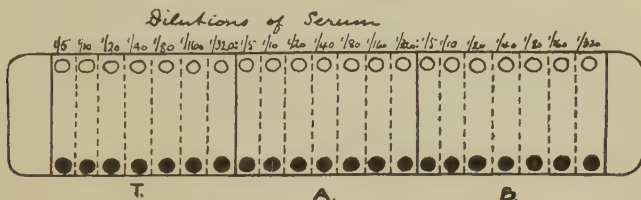


Fig. 390.—Slab with bacillary emulsions and dilutions of serum.

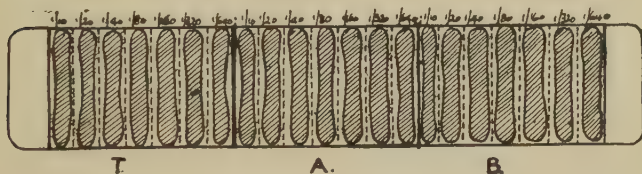


Fig. 391.—Intermingling of serum and bacillary emulsions.

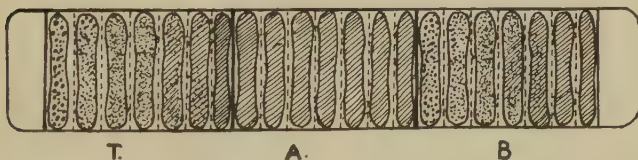


Fig. 392.—Reaction complete: showing appearances of agglutination.

Diagnosis of enteric in persons inoculated with typhoid and paratyphoid.—In this case it is necessary, should the clinical symptoms be suspicious, to test the agglutinins on several occasions during the course of the fever, to ascertain whether the titres for T, A, or B are remaining constant, rising, or falling, always remembering that the residual agglutinin titre to A after paratyphoid inoculation is a very low one.

Agglutination in undulant fever.—The agglutinins of *Brucella melitensis* and *paramelitensis* sometimes do not appear in the blood until the third or fourth week of the disease. Attention must be paid to a curious phenomenon called the *inversion phenomenon*. For instance, agglutinins may be demonstrable in the higher but not in lower dilutions. In undulant-fever cases a dilution of 1:10 on Garrow's agglutinator (or 1:40 in tubes) may be regarded as diagnostic.

Strains of *Brucella abortus* (Bang) may be agglutinated in high dilutions by patients suffering from undulant fever (see p. 272).

Certain authorities recommend that the serum of undulant-fever cases should be heated to 56° C. for half-an-hour before it is used, to eliminate any non-specific agglutinins which may be present, and this is especially applicable to fever of the *B. abortus* type, as the agglutinins of this organism can be absorbed by drinking infected milk.

The possibility of a paramelitensis infection should always be remembered, and the serum to be tested should be agglutinated against both strains of organism.

IX.—RECOGNITION OF ORGANISMS BY AGGLUTINATION

An emulsion of a pure culture of the organism is made in saline and tested on the agglutinator, or in tubes, against specific serums. In routine examinations it is convenient to keep the stock dilution of the serum (say 1:50) in small rubber-stoppered bottles in 0·5-per-cent. carbol saline. If the organism is agglutinated in a dilution of 1:100, it is tested against higher dilutions and the titre thus determined.

For special method of employing agglutination in the diagnosis of cholera, see p. 371.

Isolation of pathogenic organisms post mortem in enteric, dysentery, cholera, and plague.—In the case of the solid organs (spleen, liver, and kidney) the external surface should be seared with a hot glass rod, then incised with a sterile knife, and the pulp removed with a sterile platinum loop and plated on MacConkey or ordinary agar. In the case of the urinary and the gall-bladder the external surface should be seared as above, and a portion of the contents taken up into a sterile syringe, from which it can be transferred to the culture media.

X.—CHEMICAL AND MICROSCOPICAL EXAMINATION OF FÆCES

Reaction.—A small portion of the stool should be rubbed up in a mortar with distilled water to a soup-like consistency. A drop of the fluid should then be applied by means of a glass rod to a piece of blue or red litmus paper which has previously been moistened with distilled water.

Bile-pigment.—A small portion of the stool is mixed with a concentrated solution of perchloride of mercury, and allowed to stand 24 hours. A normal stool turns red owing to the presence of hydrobilirubin, while a green colour is indicative of unaltered biliverdin.

Benzidin test for detection of small quantities of blood in the stool.—A portion of the fæces about the size of a pea is emulsified in 5 c.c. of distilled water. The emulsion is placed in a test-tube and boiled for a minute in order to destroy any enzyme present, then cooled. An approximately saturated solution of benzidin is made by dissolving a knife-point of pure benzidin in about 2 c.c. of glacial acetic acid in a clean test-tube. Into another clean test-tube 10–12 drops of the fresh benzidin solution and from 2½–3 c.c. of hydrogen peroxide (3 per cent. H_2O_2), are poured and the tubes are slightly shaken. No green or blue tints should appear in this mixture of reagents. A few drops of the faecal emulsion are now added, when, in the presence of blood, a beautiful green, bluish-green, or blue coloration will appear. The depth of the colour and the length of time it takes to appear depend upon the amount of blood present. Later the colour changes to violet. Only a

PLATE XXXV

EGGS OF THE MORE COMMON HELMINTHS
FOUND IN MAN. × 400

- 1.—*Fasciolopsis buskii*.
- 2.—*Paragonimus ringeri*.
- 3.—*Heterophyes heterophyes*.
- 4.—*Opisthorchis felineus*.
- 5.—*Clonorchis sinensis*.
- 6.—*Loxotrema ovatum* (Yokogawa's fluke).
- 7.—*Ascaris lumbricoides* (external aspect).
- 8.— " " "
- 9.— " " (unfertilized egg).
- 10.— " " (decorticated egg).
- 11.—*Schistosoma hæmatobium*.
- 12.— " *mansoni*.
- 13.— " *japonicum*.
- 14.—*Ancylostoma duodenale*.
- 15.—*Necator americanus*.
- 16.—*Tænia solium*.
- 17.— " *saginata*.
- 18.—*Trichuris trichiura*.
- 19.—*Enterobius vermicularis*.
- 20.—*Hymenolepis nana*.
- 21.—*Dibothriocephalus latus*.
- 22.—*Heterodera radiculicola*.



J.R.FORD 22

EGGS OF THE MORE COMMON HELMINTHS FOUND IN MAN.

green or blue colour can be regarded as positive, and practice soon teaches what degree of colour-change is indicative of occult blood. It should be noted that saliva, pus, mucus, iron salts, and iodides may also give the reaction with benzidin.

Microscopical examination of the fæces for eggs of intestinal parasites.

—The eggs of the tapeworm and of the common threadworm (*Enterobius vermicularis*) (Plate XXXV, 19) are rarely found in the stools, as these parasites do not, as a rule, part with their eggs until the joints of the former, or the entire body of the latter, have left the alimentary canal. Occasionally the eggs of hepatic and intestinal parasites, such as *Schistosoma hæmatobium*, *S. mansoni*, *S. japonicum* (Plate XXXV, 11, 12, 13), *Clonorchis sinensis* (Plate XXXV, 5), *Fasciola hepatica*, *Fasciolopsis buskii* (Plate XXXV, 7), *Heterophyes heterophyes* (Plate XXV, 3), and of rarer helminths, are encountered.

The microscopical examination of fæces for eggs is by no means a difficult matter. All that is necessary, by way of preparation, is to place on the slide a minute portion of the suspected fæces—about the size of a hemp-seed—and then to apply the cover-glass, gently gliding it over the slide so as to spread out the mass in a thin, fairly uniform, and transparent layer.

The points to be attended to in the diagnosis of eggs are size, shape, colour, thickness, roughness, smoothness, and markings on the surface of the shell; the presence or otherwise of yolk spheres, of a differentiated embryo, or, in the case of the cestodes, of the three pairs of embryonic hooklets; the existence of an operculum in the case of certain trematodes and of the broad tapeworms (*Dibothriocephalus*). The eggs of the same species of parasite vary but slightly, and are in every instance sufficiently stable and definite for correct diagnosis.

Of the three common nematodes—*Trichuris trichiura* (Plate XXXV, 18), *Ascaris lumbricoides* (Plate XXXV, 7), and *Ancylostoma duodenale* (Plate XXXV, 14)—the eggs of the first are the most frequently met with. They occur sometimes in enormous numbers, as many as six or eight specimens being visible in one field of an inch-objective. They form rather striking objects under the microscope. They are oval, measuring 51 to 54 μ by 22 μ , the ends of the long axis of the oval being slightly pointed, and tipped with a little shining projection or plug. Their general appearance suggests an elongated oval tray, the projections at the poles of the ovum representing the handles of the tray. They are dark brown in colour, sharply defined, doubly outlined, and contain no differentiated embryo.

The eggs of *Ascaris lumbricoides* are considerably larger (50 to 75 μ by 40 to 50 μ) than those of *trichuris*. They are also, as a rule, more spherical or, rather, more broadly oval; occasionally they are almost barrel-shaped. Like those of *trichuris*, they are dark brown in colour from bile-staining, but they are much less sharply and smoothly defined, possessing a coarse thick shell which is roughened by many warty excrescences. The yolk contents are not so easily made out, nor, when made out, can any indications of embryo or segmentation be discovered. In certain instances the eggs are smooth on the surface, the rough outer layer being almost or altogether absent; such are supposed to be unfertilized.

A point of practical importance to be attended to lies in the circumstance that the rough outer layer of the shell of the egg of *ascaris* is very easily detached, leaving the egg with a sharp, smooth outline suggestive of some other species of parasite. To obviate this, in mounting fæces it is well to avoid too much gliding of the cover-glass over the slip.

The eggs of *Ancylostoma duodenale* contrast very markedly with both the foregoing, particularly in the matter of colour. Trichuris and ascaris eggs are invariably dark and bile-stained; those of the ancylostome are beautifully clear and transparent; they measure 55–60 μ by 32–40 μ ; have a regular, somewhat elongated oval form, with a delicate, smooth, transparent shell, through which two, or four, or eight light-grey yolk segments can be distinctly seen. It is well to search for these eggs soon after the fæces have been passed; otherwise, owing to the rapidity with which, in favourable circumstances, development proceeds, the embryo may have quitted the shell and the egg be no longer visible. The eggs of *Necator americanus* cannot be differentiated from those of *A. duodenale* with certainty. The eggs of *Trichostrongylus colubriformis* also resemble those of *A. duodenale*, but they are relatively larger and contain a fully segmented morula.

The eggs of *Heterodera radiculicola*, which have a characteristic appearance (Plate XXXV, 22), have been noted from time to time in the fæces of otherwise normal individuals since their discovery by Kofoid and White in 1919. *H. radiculicola* is a common root-parasitic nematode which lives in a variety of plants, such as radishes, celery, carrots, turnips, etc.; it is therefore liable to be encountered in the excreta of individuals who have ingested these vegetables. Of conspicuous asymmetric appearance and size, 95 μ by 40 μ , they might well be regarded in human fæces as an indication of nematode infection of the intestinal canal. A feature of the egg is the presence of two highly refractile, flattened, bluish-green globules at the poles of the embryo. As a rule they are kidney-shaped, and can pass through the alimentary canal uninjured.

The eggs of the cestodes may be distinguished from those of the nematodes and trematodes by their circular outline and, as a rule, by their smaller size.

The eggs of *T. saginata* and *T. solium* are provided with a single brown-coloured striated outer membrane, which encloses a ciliated six-hooked onchosphere (Plate XXXV, 16, 17). On the other hand, *Hymenolepis nana* eggs (40 μ) have two transparent membranes (Plate, XXXV, 20). Individual eggs of *T. saginata* are more ovoid in shape than those of *T. solium*; they measure 30 μ in diameter. The eggs of *Dibothriocephalus latus* (70 μ by 45 μ) are translucent, oval in shape, and provided with an operculum (Plate, XXXV, 21).

Method of concentrating helminth eggs.—Clayton Lane has devised a technique known as the "floatation method," which has proved accurate and useful in the mass diagnosis of ancylostome and, to a certain extent, other helminth infections, and by the aid of which a diagnosis may be determined in cases where the eggs cannot be found by direct examination of the fæces. The eggs are collected from 1 c.c. of fæces by "direct centrifugal floatation." The aim of the apparatus is to keep fixed upon the centrifuge tube a square glass cover which will collect the floating eggs, and which is held in place by a cover-clip of such a shape as to prevent movement and leakage, and yet permit of the ready removal of the cover for direct microscopical examination, thus making the area of collection and examination identical (Fig. 393). The centrifuge tube is a glass cylinder, $4\frac{3}{4}$ in. long by $\frac{1}{2}$ in. in internal diameter, closed at the bottom, and with the mouth ground off flat at right angles with the long axis of the tube. The cover is held in position during centrifuging by means of a cover-clip. The centrifuge tube is suspended in a metal bucket of $1\frac{1}{2}$ in. internal diameter. Two such buckets are employed, each containing a centrifuge tube. Fæces (1 c.c.) are first disintegrated by

vigorous shaking in water in a closed tube, and centrifuged for one minute at 1,000 revolutions; the supernatant fluid is decanted, and a solution of salt of a specific gravity of 1150 added, and centrifuging is repeated for 30 seconds at 1,000 revolutions; the tube should be so filled that the saline lies in contact with the under-surface of the cover-clip. The eggs adhere to the under-surface of the glass, which is carefully removed and examined as a "hanging-drop" preparation.

The direct centrifugal floatation method gives a greater and more reliable concentration than does any other method; the examination area is about

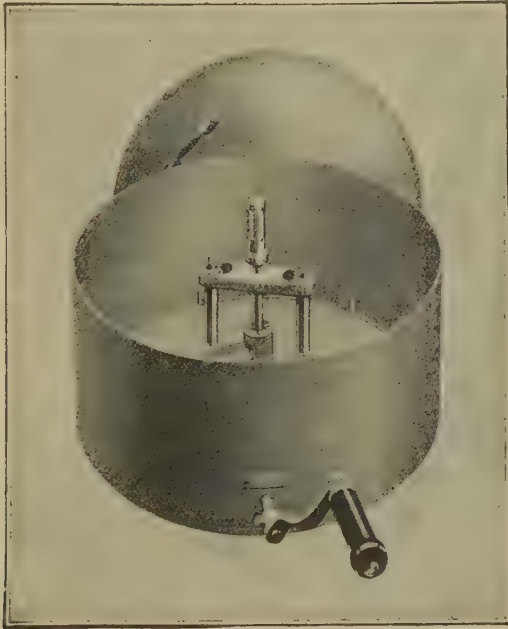


Fig. 393.—Clayton Lane's centrifuge. (*Greatly reduced. As supplied by Messrs. R. B. Turner and Co.*)

$\frac{1}{2}$ sq. in., and the whole process is carried through in a few minutes. The eggs of intestinal helminths other than the ancylostome and trichostrongylus cannot be concentrated by this method with the same certainty.

Simple floatation method (Hung).—Two grammes of fæces are carefully rubbed up with a glass rod and saturated salt-solution; the mixture is poured into a watch-glass or wide tube which is filled to the brim. A slide or cover-glass is placed in contact with the fluid and allowed to remain for 10 minutes. If ancylostome eggs are present they will be found adhering to the under-surface of the slide or cover-glass.

Fülleborn's method for detection of schistosome eggs in the fæces.—The diagnosis of intestinal schistosomiasis by detection of the eggs in the fæces by simple microscopic examination is not always an easy matter. Fæces of the volume of a hazel-nut are placed in a conical glass, carefully rubbed up with

a glass rod and a little 2½-per-cent. salt-solution, and put away to settle, in the dark, for five minutes. The solution is poured off from the sediment, and the process repeated two or three times. The schistosome eggs remain in the sediment, which is flooded with distilled water at 120° F. and exposed to a bright light.

The miracidia now escape from the eggs, and can easily be seen with a lens, particularly against a dark background. On adding a few drops of perchloride-of-mercury solution, the miracidia are killed and are found in the sediment.

“Cultivation” of ancylostome larvæ from fæces.—A piece of fæces of the size of the end of the thumb, containing numerous eggs, is mixed with one-third to one-quarter its volume of powdered charcoal, and a few drops of water are added; the mass is then wrapped in a piece of filter-paper, folded, and placed in a Petri dish in a warm, dark place for a period of one to four days. The Petri dish is now tilted, and 15–20 c.c. of sterile water poured in; the paper containing the fæces is turned over and placed so that it just comes into contact with the water. The dish is again covered up, and allowed to stand for some time, when the embryos will emerge through the filter-paper, and can be demonstrated in numbers swimming actively in the water.

“Cultivation” of ancylostomes from soil (Bærmann).—The apparatus is quite simple, and consists of a glass funnel, 8 in. in diameter, almost filled with water, of which the outlet or stem is closed by means of a clamped piece of rubber tubing. The soil sample, of which 10 oz. or even more, can be tested at a time, is placed in a brass sieve 7 in. in diameter and 3 in. in height, provided with a 1-mm. wire mesh.

The sieve containing the soil is fitted down into the funnel so that the level of the water is above that of the soil. The funnel is then held upright on a shelf by means of wooden supports and crossbars.

The soil itself should be thoroughly broken up before being placed in the sieve, and the water should be warmed to a temperature of 115° F.; in fact, it should be at least 10° F. warmer than the soil. The preparation should be left overnight, and in the morning 50 c.c. of water should be run off by means of the rubber tube and centrifuged; by these means the larvæ which have migrated into the water overnight can be found and recognized.

For identification, the larvæ should be first killed by the addition of 5 drops of a 7·5-per-cent. solution of caustic soda; the mature larvæ, both before and after losing their sheaths, can be definitely diagnosed from all other kinds of free-living nematodes in the soil by the general shape of the body, the relative length of the œsophagus, the characteristic buccal cavity, the position of the anus, and the peculiar refractivity of the cells lining the intestinal wall.

Fülleborn has devised a method which he claims is simpler than the above. A hollow wire-gauze of very fine mesh, 5 cm. in diameter, is constructed and the bottom of the same material is sewn together with thread. It is then covered with melted agar, followed by a layer of paper on which in turn is sprinkled a layer of sand. The material containing larvæ is then introduced to a height of 1 cm. The apparatus is placed in a Petri dish containing water, with the edges resting on two narrow strips of glass, and is transferred to a water bath at 50–60° C. for twenty minutes. By alternately heating and cooling, the larvæ of the *ancylostome* and *strongyloides* can be collected in the water below the agar, whilst the free-living nematodes are unable to penetrate the agar layer.

Microscopical examination and recognition of various elements in the fæces (Figs. 394, 395). *Blastocystis hominis*.—Sometimes during the examination of fæces, a yeast-like organism simulating an amœbic cyst, but less refractile, is encountered. This is known as *Blastocystis* (Fig. 394). The individual cell contains a large central vacuole, while the cytoplasm is reduced to a thin layer in which are situated one or two small iodophilic nuclei at each pole of the cyst. The cytoplasm contains refractile globules of *volutin* which must not be mistaken for the nuclei. *Blastocystis* multiplies by gemmation and rapidly increases in culture media such as are used for *E. histolytica*, unless dextrose has been added. The organism varies a good deal in size and shape; single cysts measure from 5–20 μ in diameter. The *Blastocystis* is likely to be mistaken for a fat-globule or semi-digested muscle-fibre unless the finer points of structure can be distinguished. This organism has no pathogenic significance so far as is known.



Fig. 394.—*Blastocystis hominis*. $\times 1,500$. (Orig.)

1, 2, 3, Resting forms; 4, 5, dividing forms.

Muscle-fibres, derived from meat, practically always occur in the stools, and are recognized by their cross-striation. When present in large numbers they indicate defective intestinal digestion. (Fig. 395. 2.)

Connective tissue, derived from meat, resembles mucus somewhat; it is distinguished by striation, which disappears on addition of acetic acid. When it is present in large masses, defective gastric digestion may be inferred. Elastic fibres have no significance.

Starch granules, derived from fruit and potatoes, are stained blue by addition of iodine solution. They vary in size and shape, according to the food from which they are derived. Well-preserved granules with concentric markings are seldom seen. They are often enclosed in a cellulose covering, but are not liable to give rise to much difficulty, except those derived from peas and beans, which roughly resemble the eggs of tapeworms.

The presence of excess of starch is pathological, and such a stool is usually acid and shows signs of gas-bubbles, fermentation, and presence of yeasts. It is an interesting point that starch is never bile-stained. The iodine test may be applied to ascertain the extent to which the starch has been digested. A blue colour indicates unchanged granules; red, that they have been slightly digested.

Detritus which is derived from fruits and vegetables is easily recognized by its spiral ducts, areolar tissue, vascular bundles, and pigment cells.

Neutral fats, derived from the fat of food, are recognized as colourless, highly refractile droplets, or sometimes as irregular bile-stained masses which are stained by Sudan III and are soluble in ether.

Fatty acids, derived from the fat of food, occur as sheaves of colourless

acicular crystals, which melt on being warmed and dissolve in ether. (Fig. 395, 4.)

Soaps, derived from the fat of food, occur as greasy-looking amorphous masses, or sometimes as needles which are thicker and not so long as those of the fatty acids. They may be colourless, or stained with bile-pigments. They are not soluble in ether, as are the fatty acids, and do not melt on



Fig. 395.—Microscopic appearance of common objects in the fæces.

× 800 diam. (Orig.)

- 1, Casein and fat droplets; 2, muscle-fibres; 3, soap crystals; 4, crystalline fatty needles; 5, cholesterol crystals; 6, Charcot-Leyden crystals; 7, truffle spores; 8, portions of husks of cereals; 9, hairs of wheat grain; 10, spores of fungi; 11, cells from pericarp of peas; 12, parenchyma of beans; 13, endosperm of rice; 14, vegetable spirals.

being warmed. If the film of fæces on a slide is treated with acetic acid and heated, fatty-acid crystals will be seen to separate out. (Fig. 395. 3.)

Fats may be distinguished from mucus or from vegetable material by the following rough test: Prepare a smear of the stool on a slide, put on a cover-slip, and press the latter down on to the smear: should the material be of fatty composition, the cover-slip will remain down; if vegetable

detritus or mucus, it will spring back when the pressure is taken off. (Fig. 395, 1.)

In a normal stool, fat is present almost entirely in the form of amorphous masses of soap, less often as crystals. Neutral fat ought to be absent.

Mucus occurs as transparent shreds, sometimes bile-stained. It has always a pathological significance and, when containing leucocytes and epithelial cells, indicates intestinal ulceration.

Intestinal sand.—The appearance of sand-grains in the stools of persons who live where desert conditions exist is extremely frequent, and is due to the ingestion of this substance with food.

Charcot-Leyden crystals are frequently found in stools containing entamæbæ. (Fig. 395, 6.)

Pseudo-parasites.—It frequently happens that orange-pulp is mistaken for trematodes, banana fibres for small tapeworms, pieces of cotton-thread and celery for *Enterobius vermicularis*, *Ancylostoma duodenale*, etc. As regards the microscopic diagnosis, numerous objects may be mistaken for the eggs of parasites, and it is important that the tropical worker should be able to recognize various articles of diet as they appear in the stools. The spores of truffles, which occasionally are seen in the fæces, may be mistaken for eggs of *Ascaris lumbricoides*, owing to their size (42–66 μ) and rough surface (Plate XXXV, 7). The spores of mushrooms have a similar appearance. Pollen grains of plants and spores of fungi have given rise to difficulties, in spite of their characteristic appearance under the microscope. It should be borne in mind that the pollen of conifers is often met with in the stools of people living near pine forests. No difficulty will be experienced in diagnosis when it is remembered that all these spores are really globes with a reticulated surface which can be made out on careful focusing. (Fig. 395, 10.) Occasionally cheese-mites and their eggs may be found in the fæces after being ingested with the food.

Demonstration of protozoa in fæces.—It is difficult to make out the nuclear details of the intestinal protozoa and their cysts in a fresh state. The addition of Weigert's iodine solution (iodine 1 part, pot. iod. 2 parts, water 100 parts), which has a special affinity for nuclear structure, and which renders the details much more evident, constitutes a convenient method for their recognition.

Method of concentration of protozoal cysts in fæces.—Yorke has devised the following method of concentration especially applicable to the cysts of *Entamæba histolytica*:

A mass of fæces is ground up with water in a small mortar and the emulsion shaken with 500–1,000 c.c. of water, poured into a tall glass cylinder, and allowed to stand for fifteen minutes to permit the coarser fæces material to settle. The supernatant fluid is withdrawn and centrifugalized, the deposit is shaken up with a solution of cane-sugar of specific gravity of 1080 and centrifugalized quickly. This procedure results in the separation of cysts from the remaining fæcal material. The fæces are precipitated and the cysts left floating in the supernatant fluid, which is withdrawn, diluted with about four times its volume of water, and again centrifugalized at high speed. By this means a small deposit is obtained consisting of great numbers of cysts in a relatively minute quantity of fæcal material. The deposit is then washed several times with water to get rid of all traces of sugar and the majority of the remaining bacteria.

In addition to the iodine method of demonstrating protozoa in fæces, the following methods of staining are recommended by Dobell:

Thin films of fæces are made on cover-slips and floated film downwards on the fixing fluid.

METHOD I

- (1) Fix films for 10–20 minutes in Schaudinn's fluid.¹
- (2) 70-per-cent. alcohol, two changes.
- (3) 70-per-cent. alcohol and iodine (Lugol's solution, 1 drop), 10 minutes.
- (4) Distilled water after hyposulphite-of-soda solution (1 crystal in 25 c.c.).
- (5) Hæmalum (Mayer's) 15–20 minutes.
- (6) Running water till blue.
- (7) Through alcohols, alcohol and xylol, xylol.
- (8) Mount in Canada balsam.

METHOD II

1-per-cent. hæmatein in 70-per-cent. alcohol = stain.

1-per-cent. iron alum in 70-per-cent. alcohol = mordant.²

- (1) Fix films in Schaudinn's fluid as before for 10–20 minutes.
- (2) Wash in 70-per-cent. alcohol.
- (3) 70-per-cent. alcohol and iodine, 10 minutes.
- (4) Mordant, 10 minutes.
- (5) Alcohol 70-per-cent., several changes.
- (6) Stain, 10–20 minutes.
- (7) Wash in 70-per-cent. alcohol.
- (8) Differentiate with mordant under microscope.
- (9) 70-per-cent. alcohol, several changes.
- (10) Absolute alcohol, two changes.
- (11) Absolute alcohol and xylol.
- (12) Xylol.
- (13) Mount in Canada balsam.

XI.—SPECTROSCOPIC EXAMINATION OF URINE AND OTHER FLUIDS

The spectroscopic examination of urine, extracts of fæces, and pathological exudates for the presence of recognizable spectra of blood-pigments, or their derivatives, may be performed by means of a small direct-vision pocket spectroscope. It is best to examine the urine, or fluid—which, if it contains too much pigment, should be diluted to a suitable degree—in a 6-oz. conical glass, or a test-tube, against a strong light, either artificial or natural. In the tropics, examination in the open air against a white bank of clouds will be found the most satisfactory. The size of the slit at the objective end should first be regulated so as to obtain the complete and distinct spectrum, then steadily held 1 in. from the glass and gradually moved up and down the entire length of the column of fluid.

If in doubt about the validity of a spectrum, as, for instance, in watery extracts of fæces or in urine, 100 c.c. should be shaken up well with 20 c.c. of pure amyl alcohol and a few drops of acetic acid. By collecting and filtering the supernatant fluid, the intensified spectrum may be obtained.

¹ Absolute alcohol 50 c.c., saturated solution of corrosive sublimate 100 c.c., glacial acetic acid 1–5 c.c.

² Dissolve 1 grm. of iron alum in 2 c.c. distilled water, and add 77 c.c. of 96-per-cent. alcohol.

The spectra important from a tropical point of view are those of oxy-hæmoglobin, methæmoglobin, and urobilin in the urine in blackwater fever, malaria, etc., and those of hydrobilirubin and hæmoglobin in the fæces. (Fig. 396.)

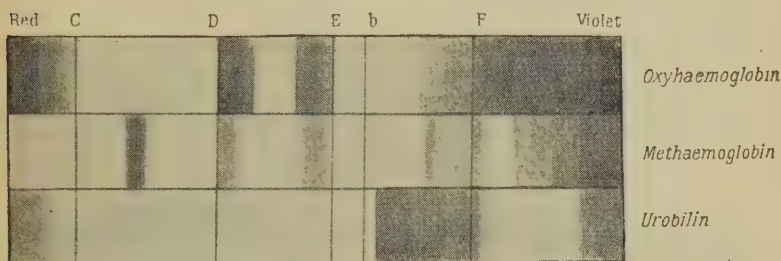


Fig. 396.—Spectra of hæmoglobin and its derivatives.

XII.—DETECTION OF SPIROCHÆTES BY DARK-GROUND ILLUMINATION AND STAINING METHODS

Detection of spirochætes by dark-ground illumination.—This is the ideal method, and is better than any other for distinguishing one spirochæte from another on morphological grounds. It consists in rendering the microscopic object self-luminous, so that no preliminary treatment is necessary. In order to achieve this, the organism should have a refractility differing from that of the medium in which it lies, and should be illuminated in such a manner that only the light reflected from the object can reach the observer's eye. It is then seen as a bright image on a dark ground. The necessary dark-ground condenser may be fitted to any microscope provided with a mechanical stage and a $\frac{1}{2}$ -in. objective.

Metal stop.—This is a funnel-shaped metal tube, inserted into the $\frac{1}{2}$ -in. objective with a view to reducing its aperture and the volume of the illuminating rays. The aperture must not exceed 0·95 mm.

The **dark-ground illuminator**, or condenser, of the latest type, is paraboloidal; two intense rays of light are made to converge on the object under observation. The best illuminator is that supplied by Leitz.

Cover-glasses and slides.—The slides should be 1 mm. thick, and the cover-glasses No. 1, for use with the Leitz instrument, but the thickness varies with the make of the microscope. All makers state a certain length of tube for which their objectives are corrected, usually 160–170 mm. This is dependent on the thickness of the cover-glass used. The thickness usually allowed for is 0·15–0·18 mm. If the cover-glasses in use are thicker than this, the tube should be shortened; if thinner, lengthened.

Illuminant.—The selection of a suitable illuminant is a most important point. Wherever obtainable, electric light gives the best illumination, especially the lamp, made by the Ediswan Company, known as the "Pointolite." This lamp, fitted with a special hood and adjustable condenser, supplied by Hawksley & Sons, Wigmore Street, London, W.1., is most effective. But apparatus such as the above is not always obtainable in the tropics. Fairly good results may be obtained by using an inverted incandescent gas-burner, but generally the quantity of light available is not sufficient. An acetylene bicycle-lamp may also be used with fairly

satisfactory results, but in using the substitutes for electric light the rays must always be intensified by means of a strong bull's-eye condenser placed some distance in front of the light.

Manipulation.—Whichever illuminant is used, the microscope should be placed in the vertical position, about 8 in. from the source of light, so that the maximum intensity of the rays may impinge upon the plane mirror. The first step consists in centring the condenser under the low power $\frac{2}{3}$ -in. lens; for this purpose it should be racked up to the level of the stage. On focusing, it will be observed that the condenser is engraved with two concentric circles, which should be accurately centred by means of the screws provided for this purpose. It should then be racked down about an inch below the level of the stage, and a drop of cedar-wood oil, free from bubbles, placed on the upper

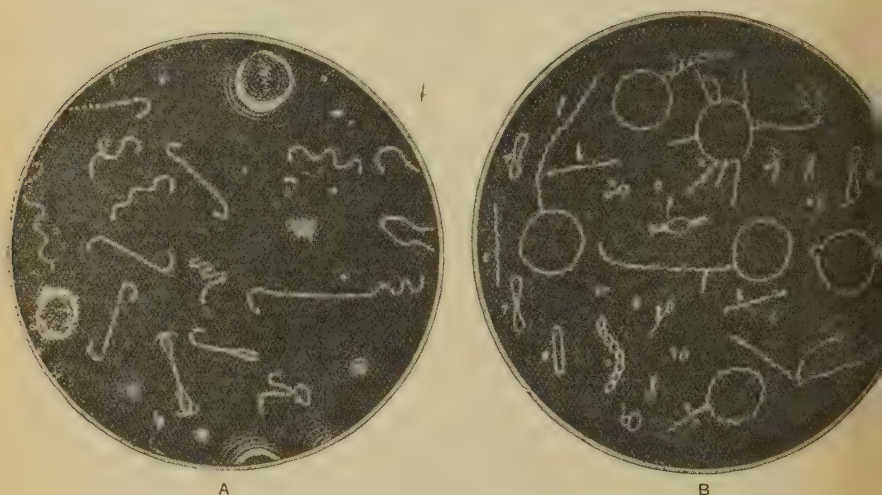


Fig. 397.—Two dark-ground fields, illustrating puzzles and fallacies in blood examination. $\times 1,000$.

- A. Dark-ground appearance of a field containing *Leptospira icterohaemorrhagiae* from a culture in blood medium. (After Wenyon, "Trop. Dis. Bull.")
- B. Appearance of elements in blood under dark-ground illumination showing "pseudospirochaetes." (After Knowles and Das Gupta, "Ind. Med. Gaz.")

surface of the condenser as well as on the under-side of the preparation, and the latter placed upon the stage. When this has been effected, the condenser is gently racked up until the oil comes into contact and spreads evenly upon the under-surface of the slide. The observer should then ascertain through the low power that a definite *ring of light* of great intensity illuminates the preparation. At first this appears in the form of a circle with a dark centre, and by manipulating the mirror it can be focused exactly in the centre of the field. The condenser should then be racked up or down, as the case may be, until the black centre is replaced by an evenly illuminated spot. A drop of cedar-wood oil should be placed on the upper surface of the preparation, and the $\frac{1}{2}$ -in. lens carefully racked down until it comes in contact with the oil. Further focusing should be done with the fine adjustment.

Perfect cleanliness is necessary for success; the cover-glasses and slides must be absolutely free from defects, and protected from dust.

In order to obtain the best effect, the room should be darkened. The microscopic field should be absolutely black, and the spirochætes and micro-organisms should appear as bright specks upon a dark ground.

In order to test the adjustment of the apparatus, a fresh preparation, obtained from the mouth or from a hollow tooth may be used, in which large numbers of *Treponema dentium* are usually present. Fig. 397 shows the appearance of *Leptospira icterohæmorrhagiæ* by this method and, by contrast, the fallacious appearance of normal blood.

Stained films.—To obtain the best results, it is essential that the film be properly fixed *the moment it dries*, preferably by absolute alcohol or methyl-alcohol. The film may then be stained by one of the following methods:

1. *Giemsa's ordinary or long method.*—Cover the slide with a 1:10 to 1:15 dilution of Giemsa's stain in tap-water, and leave for 12 hours. Wash, dry, and examine.

2. *Giemsa's rapid method.*—In this method the same dilution of Giemsa's stain is employed as in the first, only the stain is poured on the slide and the latter is held over a flame until the steam rises. This process is repeated three or four times, the last application of stain lasting 2 minutes. The slide is then washed with water, dried, and examined.

Fontana's method for staining spirochætes in smears.—Smears must be air-dried, not fixed by heat. The fluid, mordant, and stain are:

Hugo's fluid.

Acetic acid	1 c.c.
Formalin	20 "
Aq. dest.	100 "

Mordant.

Tannic acid	5-per-cent. in
Carbolic acid	1 " "

Silver stain.

Silver nitrate 0.25 per cent. in distilled water. Add ammonia drop by drop until slight turbidity is produced. Excess of ammonia clears the solution and renders it useless.

1. Cover films with Hugo's fluid; flood several times.
2. Wash in water.
3. Cover with mordant. Heat slide till steam rises, and allow to act 30 secs.
4. Wash in water and, without drying,
5. Pour on silver stain. Heat till steam rises. Allow to act 30 secs. Wash in water, dry. The spirochætes are stained black. brownish to

XIII.—METHODS OF PRESERVING HELMINTHS AND THEIR EGGS

Trematodes.—The flukes should be collected into a test-tube containing 1 in. of 0.85-per-cent. saline. This should be shaken vigorously for several minutes in order to stun them and render them flaccid. When extended they should be killed by the addition of an equal quantity of a saturated

solution of mercury perchloride (HgCl_2). The flukes should then be washed in plain water for 20 minutes. For storage purposes they must be placed in tubes containing 70-per-cent. alcohol.

Cestodes.—After removal from the stool, tapeworms should be allowed to relax in water—a process which may last 2–24 hours, according to the size of the worm. They are then killed and fixed in hot Schaudinn's fluid (*see* p. 882). After fixation, wash in water for 1–24 hours, according to the size of the specimen, and subsequently store in 70-per-cent. alcohol.

Nematodes.—These should be collected into 0.8-per-cent. saline solution, not into plain water. After removal of faecal matter by shaking, they should be dropped into 70-per-cent. alcohol heated to 80°C. , to which has been added 5-per-cent. glycerin. When cool, they may be stored in this same solution.

Eggs of trematodes, cestodes, and nematodes.—A small portion of the stool containing the eggs should be thoroughly mixed by stirring with an equal quantity of Langeron's lactophenol (phenol 1 part, lactic acid 1 part, glycerin 2 parts, water 1 part). Permanent microscopic preparations of eggs in this medium may be made by ringing the cover-glass with the following preparation, which should be applied after melting by heat: Beeswax 3 parts, Venetian turpentine 1 part, or with "seccotine."

XIV.—METHODS OF REARING, DISSECTING, AND PRESERVING MOSQUITOES

Collecting.—Hibernating mosquitoes required for experimental work are easily collected with the aid of a glass bottle (a pickle bottle serves admirably), through the cork of which the upper half of an ordinary test-tube is inserted (*see* Fig. 398).

A piece of blotting-paper in the bottle acts as a perch for the mosquitoes; they might otherwise be damaged by the water of condensation which collects if the bottle is held in the hand for any length of time.

Caging.—A convenient cage may be made from a small wooden box about $1\frac{1}{2}$ ft. by 1 ft. The bottom is removed and the sides are used as roof and floor. One end is taken out, and from it two strips 1 in. wide are cut, and nailed at the bottom end, to support the roof and floor. A sheet of white paper is then gummed to the floor. At both sides mosquito netting is attached and stretched, being held in position with gum or seccotine (Fig. 399). A basin of fresh water containing some floating grass is placed inside the cage, in which the insects may deposit their eggs. A little liquid glucose on a pad of cotton-wool, placed on a gauze-covered aperture in the roof of the cage, serves admirably as a source of food, as insects imbibe the liquid from underneath, and do not become soiled thereby. The liquid glucose must be renewed daily. Before eggs are deposited a feed of mammalian blood appears to be necessary, for which a tame rabbit may be conveniently utilized. When required, individual insects are readily removed from the cage with the aid of a test-tube. Considerable difficulty will be experienced in rearing the larvæ of anopheles from the eggs deposited by the adult insects. In order to do this, an effort should be made to obtain natural water from the ditches and swamps in which these insects breed, and also a supply of confervæ and spirogyra upon which the larvæ feed, but they thrive best on a proprietary preparation called piscidin.

Dissection.—After killing the mosquito with chloroform, the legs and wings should be removed, and the body placed on a slide containing a drop

of normal saline. Put the slide under a dissecting microscope and, with the aid of two fine surgical needles mounted in wooden handles, carefully remove the head by holding the thorax with one needle and gently exerting traction on the head with the other. The salivary glands are generally adherent to the head and can be "snicked" off. If such is not the case, carefully remove a portion of the chitinous surface of the thorax; then, by fixing the lower part with one needle, the protruding glands are gently withdrawn with the other. To remove the stomach, "snick" each side of the last abdominal segment, grasping the upper part of the abdomen with the left needle, and withdraw the viscus with the right. The stomach and salivary



Fig. 398.—Bottle for collecting live mosquitoes. (*A. Michieli.*)

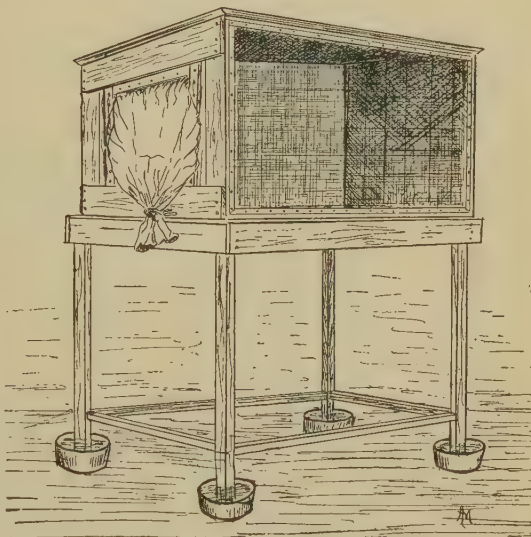


Fig. 399.—Cage for rearing and storing living mosquitoes. (*A. Michieli.*)

glands, which must not be allowed to dry, are then covered with a cover-slip and examined under a low power of the microscope. (Fig. 400.)

Mounting.—Various methods of mounting mosquitoes have been described, but perhaps the simplest is the cardboard-disc method. Good results can only be obtained if the fly has been recently killed.

The specimen for mounting is laid on its back on a sheet of cork. A fine entomological pin is then gently pushed through a circular cardboard disc, with the aid of entomological forceps, so that half the pin protrudes on either side. The sharp end is pushed through the centre of the thorax. The pin is then gently pulled down so that the insect lies flush with the card. With the aid of a mounted needle the legs are carefully arranged; this done, a larger pin is inserted into the top of the disc, and in this manner the disc is pinned into a storing box.

A cigar-box, the bottom of which is covered with dental wax, or fitted with sheet cork as above, serves admirably as a storing box for mosquitoes.

If naphthaline is not used, a piece of cotton-wool soaked in creosote and pinned into a corner of the box will prevent the growth of moulds.

Celloidin sections.—In order to obtain satisfactory microscopic sections of mosquitoes they must be cut in celloidin. To do this the following points must be observed :

1. Drop alive into 70-per-cent. alcohol.
2. Remove legs and wings 24 hours after.
3. Place in fresh alcohol 90-per-cent., 24 hours.
4. Ether and alcohol (equal parts), 24 hours.
5. Thin celloidin (dissolved in ether and alcohol, equal parts), 24 hours.
6. Thick celloidin, 24 hours.

In order to mount, pour thick celloidin on the surface of a wooden block, allow a skin to form, drop the mosquito in lightly and allow it to sink and set thoroughly, then put into 60-per-cent. alcohol and leave for 12 hours.

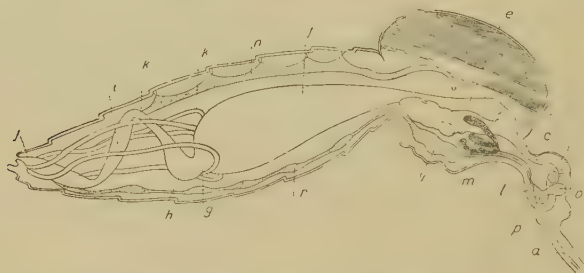


Fig. 400.—Section of mosquito.

a, Mouth ; *b*, pumping organ ; *c*, cesophagus ; *d*, homologue of proventriculus ; *e*, anterior part of midgut ; *f*, midgut ; *g*, pylorus ; *h*, pyloric diverticulum ; *i*, hindgut ; *j*, rectum ; *k*, Malpighian tubes ; *l*, salivary duct ; *m*, salivary gland ; *n*, dorsal vessel ; *o*, supraesophageal ganglion ; *p*, subesophageal ganglion ; *q*, conjoined ganglia ; *r*, abdominal ganglia.

Cut sections on a sliding microtome provided with a large sharp blade, and with the aid of a camel's-hair brush remove the sections from the razor (which should be kept wet), float in spirit, and wash in water several times.

1. Stain with acid hæmatoxylin (Ehrlich's), 10–15 minutes.
2. Blue in water.
3. Wash for 1 minute in 1-per-cent. acid alcohol.
4. Blue again in water.
5. Counterstain with watery eosin, $\frac{1}{2}$ minute.
6. Wash rapidly through alcohols 40-per-cent., 50-per-cent., and 90-per-cent.
7. Leave for 10 minutes in 90-per-cent. alcohol.
8. Clear in carbol xylol (30-per-cent. phenol in xylol).
9. Leave in fresh carbol xylol for 15 minutes.
10. Mount in Canada balsam.

The mosquitoes, from the beginning of the process, must not be allowed to dry. Neither absolute alcohol nor clove oil can be used.

Wenyon stains the tissue *en masse*, after removal of the exoskeleton, in diluted Mayer's acid hæmalum for 12 hours, after fixation. Subsequently the tissue is embedded in paraffin and cut.

To obtain sections of the salivary gland, dissect out the contents of the thorax after removal of the head. The muscular mass containing the gland is fixed and treated as above.

XV.—SCALES AND STANDARDS

Centigrade and Fahrenheit scales.—To convert Fahrenheit into Centigrade, subtract 32, multiply the remainder by 5, and divide the result by 9.

To convert Centigrade into Fahrenheit, multiply by 9, divide by 5, and add 32.

The diagram (Fig. 401) shows the relation of Fahrenheit to Centigrade degrees.

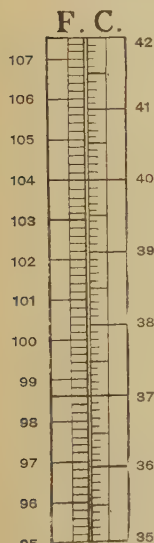


Fig. 401.

Fahrenheit and
Centigrade scales
compared.

RELATION OF THE METRIC TO THE IMPERIAL STANDARD

Standards of mass

1 milligramme	=	0.015 grain approximately.
1 centigramme	=	0.154 " "
1 decigramme	=	1.543 grains "
1 gramme	=	15.432 " "
1 kilogramme	=	35 oz., 120 grains, or 15,432 grains.

Standards of capacity

1 cubic centimetre	=	17 minims approximately.
1 litre	=	37 fl. oz., 1 fl. dr., 34 min. approximately.

Standards of length

1 micron (μ)	=	0.001 millimetre, or 0.000039 inch.
1 millimetre	=	0.039 inch.
1 centimetre	=	0.393 "
1 decimetre	=	3.937 inches.
1 metre	=	39.37 " nearly.

INDEX

A

- Abortus fever, 269, 272
- Abramis brama, 718
- Abscess, filarial, 550
 - of brain, amœbic, 434
 - of epididymis, amœbic, 435
 - of liver, amœbic (*see* Liver abscess)
 - of spleen, amœbic, 435
- Acalyptophis, 848
- Acanthocephala, characters of, 791
- Acanthocheilonema perstans, 535, 756, 784
 - characters of, 784
 - embryo of, 785
 - geographical distribution of, 784
 - life-history of, 785
 - pathogenesis of, 786
- Acanthophis, 853
- Acarina, 792
- Acarine dermatosis, 658
- Acarus balatus, 794
- Accès pernicieux, 39
- Acids, fatty, in feces, 879
- Ackee poisoning, 606
- Acocanthera, 604
- Aconitum ferox, 605
- Acrocephalus orientalis, 230
- Actinomycoïtic mycetoma, 338
- Adenium, 604
 - boëhmianum, 604
- Adler's culture medium, 864
- Adynamic remittent fever, 38
- Aedes (genus), 671, 814
 - albopictus, 814, 816
 - argenteus, 190, 205, 671, 706, 814, 815
 - and dengue, 205
 - and yellow fever, 190, 192, 193, 194
 - nomenclature of, 671
 - chemulpcensis, 776
 - generic characters of, 814
 - togoi, 776
 - variegatus, 542, 775, 776, 816
- Æstivo-autumnal fever (*see* Malaria fever, subtertian)
- African human trypanosomiasis (*see* Sleeping sickness, gambiense; Sleeping sickness, rhodesiense)
- Agamofilaria streptocerca, 573 (foot-note), 788
- Agamonematodum migrans, 619
- Agar, cystine, composition of, 265
- Agave americana, 608
- Agglutination in cholera, 365, 371
 - in enteric and enteric-like fevers, 291
 - — — — — technique of, 868
 - fever by Dreyer's drop method, 869
 - by Garrow's agglutinometer, 870
- Agglutination in enteric fever by progressive dilution of serum, 868
 - in infectious jaundice, 186
 - in melioidosis, 268
 - in subjects inoculated with typhoid and paratyphoid, 873
 - in typhus fever, 223, 868
 - in undulant fever, 274, 873
 - inversion phenomenon in, 873
 - of Brucella abortus in undulant-fever patients, 873
 - recognition of organisms by, 874
 - units, standard, 869
- Aglypha, 847
- Agouti and leishmaniasis americana, 160
- Ague, atypical, 32
 - "—cake," 65
 - fit (*see* Malaria fever, typical)
- Ainhum, 661
- "Aino," 687
- Aipysurus, 848
- Akamushi, 229
- Aker lampong, 605
- Akis spinosa, 749
- Akta, 606
- Alastrim, 299
 - distribution of eruption in, 301
 - epidemiology of, 300
 - etiology of, 299
 - geographical distribution of, 299
 - incubation period of, 300
 - pathology of, 300
 - prophylaxis of, 301
 - — by vaccination, 301
 - rash of, 300
 - symptoms of, 300
 - treatment of, 301
- Alcohol poisoning, 608
- Aldehyde test in kala-azar, 146
- Aleppo boil, 151
- Alpine scurvy, 346
- Amaas, 299
- Amblycephalidæ, 847
- Amblyomma, 796
- Amblyopia, malarial, 39
 - diagnosed from quinine amblyopia, 40
 - quinine, 71
- Ambulatory cholera, 369
- American trypanosomiasis (*see* Trypanosomiasis, South American)
- Amitosis, 673
- Amœba limax, 680
 - (*see also* Entamœba)
- Amœbæ, intestinal, commoner, differential characters of, 678
- Amœbiasis, 402
 - "Amœbic diarrhœa," 409
 - dysentery (*see* Dysentery, amœbic)
- Anæmia, acute hæmolytic, in subtertian malaria, 42
 - in sprue, 445
- Ankahré, 496
- Anaplasma centrale, 704

- Anaplasma marginale*, 704
Ancylostoma braziliense, 756, 760
 — *ceylanicum*, 721, 760
 — *duodenale*, 589, 756, 759
 — description of, 589, 759
 — eggs of, in feces, 875, 876, and Pl. xxxv, facing p. 874
 — embryos of, 590
 — geographical distribution of, 589, 759
 — reproduction and mode of infection of, 590
Ancylostome dermatitis, 601
 — larvæ, "cultivation" of, from feces, 878
Ancylostomes, "cultivation" of, from soil, 878
Ancylostomiasis, 589
 — diagnosis of, 595
 — etiology of, 589
 — geographical distribution of, 589
 — history of, 589
 — modes of infection with, 590
 — parasites of, 589
 — pathology of, 591
 — prophylaxis of, 598
 — Rockefeller Commission and, 589 (footnote), 600
 — symptoms of, 592
 — treatment of, 596
 — by beta naphthol, 598
 — by carbon tetrachloride, 597
 — by chenopodium oil, 596
 — by eucalyptus oil, 598
 — by tetrachlorethylene, 598
 — by thymol, 596
 "Angareeb," 306
Angiostomidae, 756
Animal parasites and associated diseases, 511
 — poisons, 609
Anisocytosis, 862
Anisolabis anulipes, 749
Ankistrodon, 855
Anopheles aconitus, 812
 — *albimanus*, 4
 — *algeriensis*, and *Filaria bancrofti*, 779
 — *costalis*, and *Filaria bancrofti*, 779
 — *crucians*, 812
 — *culicifacies*, 19
 — *funestus*, 811
 — *gambiæ*, 779
 — generic characters of, 810
 — *hyrcanus*, 812
 — *maculipennis*, 19, 20, 806, 807, 811, 812
 — *quadrinaculatus*, 20
 — *rossi*, 812
 — and *Filaria bancrofti*, 776
 — *stephensi*, 20
Anophelines and transmission of malaria, 812
 — artificial infection of, with malaria, 20
 — natural infection of, with malaria, 19
Anophelini, species of, known to carry malaria parasites, 813
Anoplura, 834
Antiarin, 604
Antiaris toxicaria, 604
Anti-hookworm campaign, 600
Antileprol, 481
Antimony compounds, for intravenous injections, 665
 — in dracontiasis, 580
 — in filariasis, 567
 — in kala-azar, 148
 — in leishmaniasis americana, 162
 — in leprosy, 482
Antimony in oriental sore, 157
 — in schistosomiasis, 519, 527, 534
 — in trypanosomiasis, 118, 119, 125
 — in ulcerative granuloma, 509
Antityphoid inoculation, 295
Antivenene, 612
Aphthæ tropicæ, 440
Apistocalamus, 852
Apocynaceæ, 605
Aponomma, 796
Appendicostomy in bacillary dysentery, 381
Arachnida, 614, 792
Araneæ, 615
Arctomys bobac, 245
 — "Ardent fever" and malaria, 39
Areca catechu, 608
Argentina, 795
Argas, 795, 796
 — *miniatus*, 799
 — *persicus*, 163 (footnote), 797, 799
Argochrom, 279
Armadillo, 686, 839
Arrow poisons, 604
Arrow-poisoned wounds, treatment of, 605
Arsenic in pellagra, 356
 — in trypanosomiasis, 117
Arthritis in bacillary dysentery, treatment of, 398
Arthropoda, classes of, of medical interest, 792
Artificiosostomum sufaratyfex, 722
Ascariasis, 587
 — diagnosis of, 587
 — symptoms of, 587
 — treatment of, 588
Ascaridæ, 756
Ascaris lumbricoides, 587, 588, 757
 — characters of, 757
 — eggs of, in feces, 875, and Pl. xxxv, facing p. 874
 — geographical distribution of, 757
 — habit of, 757
 — life-history of, 757
Ascaron, 587
Asclepias, juice of, 605
Aspergillus bouffardi, 639
 — *fumigatus*, 349
 — *nidulans*, 638
 — *niger*, 349
Aspidelaps, 850
Astacus japonicus, 721
Asturian rose, 346
Asylum beriberi, 323
Atheris, 854
Atoxyl in pellagra, 357
 — in trypanosomiasis, 117
Atractaspis, 854
Atriplex littoralis, 606
Atriplicism, 606
Atropine, 605
 — test in enteric fevers, 292
Atypical agues, 32
Auchmeromyia, 804
 — *luteola*, 620, 828
Auremetine, 416
Austen's classification of Glossinæ, table facing p. 824
Autumn fever, 188
Axoneme, 673

B

- Babesia bigemina*, 703
 — *caballi*, 703
 — *canis*, 703
 — generic characters of, 703

- Babesia mutans*, 703
 Baccelli's mixture, 75
 Bacillary dysentery (*see* Dysentery, bacillary)
Bacillus aertrycke (supester) fever, 297
 — colic infections, 297
 — dysenteriae, 380
 — and allied organisms, morphological and cultural characters of, 382
 — Flexner-Y, 380, 383
 — morphological and cultural characters of, 382
 — isolation of, during life, 391
 — post mortem, 392
 — Shiga, 380, 382
 — and allied organisms, morphological and cultural characters of, 382
 — enteritidis fever, 297
 — fecalis alkaligenes septicaemia, 296
 — leprae and tubercle bacillus, resemblances and differences between, 467
 — characters of, 467
 — discovery of, 465
 — experimental inoculation with, 466
 — staining of, 467
 — mucosus capsulatus, 505
 — of cholera (*see* Comma bacillus)
 — paratyphosus-A, -B, -C, 282, 284
 — pestis, 239
 — characters of, 241
 — culture of, 241
 — differentiation of from *B. pseudotuberculosis rodentium*, 256
 — discovery of, 241
 — modifications of virulence of, 242
 — *pseudotuberculosis rodentium* and *B. pestis*, 256
 — rickettsiiformis, 226
 — typhosus, 282, 283, 284
 Bacterial dysentery (*see* Dysentery, bacillary)
 Bacteriophage, 397
 — d'Herelle's, 391
 Bacterium tularense, 264
 — whitmori, and melioidosis, 267
 Bael fruit in sprue, 453
 Baermann's technique for "cultivation" of ancylostomes, 878
 Balantidial dysentery, 436
Balantidium coli, 668, 436, 706
 — minutum, 708
 Bandi's method of identifying comma bacillus, 371
 — — — — — Davies's modification of, 371
 Banti's disease, 528
 Barbeiro, 131
 Barbiers, 321
Barbus barbus, 718
 Barcoo rot, 627
 Barlow's disease, 359
 Barracouta, 614
Barringtonia speciosa, 605
Bartonella bacilliformis, 233, 704
 — and Oroya fever, 233
 — and verruga peruana, 233, 236
 — muris, 234, 704
 Basophiles, 862
 Bass's method for cultivation of malaria parasite, 865
 — — — — — Sinton's modification of, 866
 Batavia powder in sprue, 457
 "Bayer 205," 120
 — — — — — for intravenous injection, 666
 — — — — — in gambiense sleeping sickness, 120, 121
 — — — — — in rhodesiense sleeping sickness, 125
 Bed-bugs, 836
Belascaris cati, 756
 Benign tertian fever (*see* Malaria fever, tertian)
 Benzidin test for blood in faeces, 874
 Beriberi, 321
 — age and, 322
 — asylum, 323
 — cardiac attacks in, 335
 — climatic conditions and, 322
 — diagnosis of, 338
 — differential, 338
 — of gambiense sleeping sickness from, 115
 — dropsical cases of, 333
 — "dry" cases of, 329
 — epidemiology and endemology of, 322
 — etiology of, 323
 — food-deficiency theory of, 323
 — geographical distribution of, 321
 — history of, 321
 — infantile, 322, 336
 — treatment of, 341
 — mortality of, 336
 — occupation and, 322
 — overcrowding and, 322
 — paraplegic cases of, 329
 — pathology of, 327
 — polyneuritis of fowls and, 324
 — prognosis of, 339
 — prophylaxis of, 342
 — sex and, 322
 — ship, 322
 — symptoms of, 329
 — treatment of, 340
 — uncertain course of, 335
 — vitamins and, 326
 Berne, 834
 Besredka, and immunization against cholera, 378
 Beta-naphthol in ancylostomiasis, 598
 Betel, 608
 Bhang, 608
 "Bicho Colorado," 794
 Big heel, 663
 Bile pigment in faeces, detection of, 874
 Bilharzia disease, 511
 Bilharzial dysentery, 436
 Bilharziasis, 511
 Bilharziosis, 511
 Biliary cirrhosis, infantile, 463
 Bilious remittent malaria, 38
 — — — — — diagnosis of, from yellow fever, 67
 — — — — — treatment of, 83
 — — — — — typhoid of Griesinger, 164
 Biological protein value, 351
 Bismuth in amoebic dysentery, 418
Bitis nasicornis, 801
 — spp., 854
 Black fever, 224
 — sickness, 132
 — spores, Ross's, 18
 — vomit in yellow fever, 198
 Blackwater fever, 44
 — — — — — and malaria, 44
 — — — — — blood in, 63
 — — — — — cases in England, features of, 45
 — — — — — diagnosis of, 66, 68
 — — — — — differential, 68
 — — — — — distribution of, geographical, 44

- Blackwater fever, distribution of, topographical, 44
 ———— epidemiology of, 45
 ———— etiology of, 45, 49
 ———— malaria theory of, 46
 ———— quinine theory of, 46
 ———— specific theory of, 46
 ———— gall-bladder in, 62
 ———— hæmolytic in, mechanism of, 48
 ———— incubation period of, 50
 ———— mortality of, 53
 ———— nursing in, 86
 ———— onset of, 51
 ———— pathology of, 62
 ———— pre-blackwater state in, 50
 ———— predisposing causes of, 47, 52
 ———— prognosis of, 69
 ———— prophylaxis of, 99
 ———— seasonal incidence of, 48
 ———— subsequent attacks of, 52
 ———— symptoms of, 50
 ———— treatment of, 84
 ———— urine in, 52
 Blanfordia, 732
 Blastocystis hominis, examination of
 ———— faeces for, 879
 Blastomycosis, 642
 ———— diagnosis of, 643
 ———— pathology of, 643
 ———— treatment of, 644
 ———— types of, 642
 Blatta germanica, 749
 Blepharoplast, 672
 Blighia sapida, 607
 Blood flagellates (*see* *Hæmoflagellata*)
 ———— spirochaetes, diseases due to, 164, 181
 ———— (*see* *Treponema*; *Leptospira*)
 ———— transfusion, intravenous, technique of, 668
 Blood-cells, red enumeration of, by Thoma-Zeiss hæmocytometer, 863
 ———— polychromatic degeneration of, 862
 ———— varieties of, significance of, 861
 ———— white, enumeration of, by Thoma-Zeiss hæmocytometer, 863
 Blood-culture for enteric organisms, etc., technique of, 866
 Blood-films, for demonstration of filarial embryos, 859
 ———— of flagellated body in malaria, 860
 ———— for differential count of cells, staining of, 859
 ———— for protozoa, staining of, 859
 ———— for study of fresh blood, 859
 ———— malarial, staining of, 63
 ———— thick, preparation of, 857
 ———— thin, preparation of, 857
 Blood-platelets, 862
 Blue disease, 224
 Bluebottle, 804
 Bodo caudatus, 692
 Bodonidæ, 692
 Boeck and Drbohlav's culture medium, 865
 Boidæ, 847
 Boils, 629
 ———— treatment of, 630
 "Bolus alba," 373
 Boophilus decoloratus, 796
 Bos sinicus, 729
 Bosch yaws, 160
 Boubas, 486
 Bouffard's black mycetoma, 639
 ———— white mycetoma, 640
 Boulengerina, 850
 Bouton de Bagdad, 151
 ———— de Biskra, 151
 ———— d'Orient, 151
 Brachyaspis, 853
 Brachyurus calvus, 699
 "Brassy bodies," 27, 48
 Breakbone fever, 205
 Bright's disease, malaria and, 57
 Brill's disease, 219, 222
 Brood-capsules, 751
 Brucella abortus, 269, 272
 ———— agglutination of, in undulant fever patients, 873
 ———— and *Brucella melitensis*, 269, 273
 ———— melitensis, 269, 271, 273
 ———— paramelitensis, 271
 Brumpt's white mycetoma, 639
 Bupas braziliæna, 160
 Bubo, climatic, 659
 Bubonic plague (*see* *Plague*)
 Buffalo-gnats, 803, 820
 Bugs, 835
 ———— destruction of, 836
 Bullinus africanus, 517, 725, 727, 731
 ———— and *Schistosoma hæmatobium*, 512
 ———— contortus, 522, 725, 727, 731
 ———— dybowskii, 725, 727, 731
 ———— innesi, 725, 727, 731
 ———— truncatus, 727, 731
 Bungarus, 850, 851
 ———— fasciatus, 609, 612
 ———— spp., 848, 849
 Burdwan fever, 132
 Bushbuck, 104
 Buthus martensi, 614
 ———— maurus, 614
 "Butolan," 768
 Bythinia striatula var. japonica, 717

C

- Cachexia, malarial (*see* *Malarial cachexia*)
 Cæcostomy in bacillary dysentery, 400
 Calabar swellings, 571
 Calliphora, 804
 ———— vomitoria, 621
 Callophis, 851
 Calymmatobacterium granulomatis, 505
 Cambaroides similis, 721
 "Canguary," 126
 Cannabis indica, 608
 ———— sativa, 608
 Caraate, 650
 Carapata disease, 167, 176
 Carassius auratus, 717
 Carbon tetrachloride in ancylostomiasis, 597
 ———— in cestode infection, 602
 Carbon-dioxide snow in leprosy, 482
 ———— in oriental sore, 159
 Carcinoma, gastric, Spiroptera neoplasticæ and, 755
 Carriers of bacillary dysentery, 390
 ———— of cholera, 376
 ———— of enteric fever, 283
 ———— detection of, 291
 Carrion's disease, 233
 Carter's black mycetoma, 639
 Casoni test in diagnosis of hydatid disease, 752
 Cassia alata, 646
 Castellani, and discovery of parasite of sleeping sickness, 101
 Cat-bite disease, 215
 Causus, 854
 Celloidin sections of mosquitoes, 888
 Centigrade and Fahrenheit scales, relation between, 889
 Centipedes, bites of, 616

- Central neuritis of Jamaica, 345
 Centrifugal floatation method of concentration of fæces, 876
Centropus javanicus, 230
 Centrosome, 672
Centrurus, 614
Cephaelis ipecacuanhæ, 413
Cerastes, 854, 855
Ceratophyllus acutus, 265
 — fasciatus, 248, 688, 749
Cerbera odollam, 605
Cercaria indicæ, 736
 — schistosome, structure of, 736
 — stage of *Schistosoma hæmatobium*, 726
Cercariæ, 712, 736
 — amphistome, 736
 — classification of, 736
 — distome, 736
 — echinostome, 736
 — fork-tailed, 736, 737
 — furcocercous, 736
 — gasterostome, 736
 — leptocercous, 736
 — lopho-, 736
 — microcercous, 736
 — monostome, 736
 — schistosome, measurements of, etc., 739
 — xiphidio-, 736
Cercocæbus fuliginosus, 683, 723
Cercocystis, 748
Cercomonas longicauda, 692
Cercopithecus, 167, 699
 — albigularis, 801
 — and sleeping-sickness inoculations, 116
 — callitrichus, 735
 — patas, 103
 — pousarguei, 801
 Cerebral capillaries, embolism of, in malaria, 40
 — forms of subtertian malaria, 39
 Cerebro-spinal fever, rash of, 317
 — fluid, examination of, 868
 — in diagnosis of gambiense sleeping sickness, 116
 Cestodes, 601, 711, 739
 — characters of, 739
 — eggs of, Pl. xxxv, facing p. 874
 — preservation of, 885
 — treatment of affections due to, 602
 Ceylon sore mouth, 440
 Chagas' disease (*see* Trypanosomiasis, South American)
Chætopenma olivacea, 616
 Chapenonada, 205
 Charcot-Leyden crystals in fæces, 881
 Chaulmoogra oil in leprosy, 480, 482
 Cheese-mites, 793
 Cheloid, 623
 Chenopodium oil in ancylostomiasis, 596
 — in cestode infection, 602
Cherodon rupestris, 837
 — and South American trypanosomiasis, 131
Chiatopsylla rossi, 246
 Chick and Hume, and diet in pellagra, 352
 Chilomastix in bacillary-dysentery exudate, 391
 — mesnili, 693, 694
 — and dysentery, 438
 Chilopoda, 616
 Chigger, 654
 Chironomidæ, 803, 809, 821
 — differentiation of, from mosquitoes, 809
 Cholera, 362
 — agglutination in, 371
 — algid stage of, 368
 — ambulatory, 369
 — carriers, 376
 — diagnosis of, 370
 — — bacteriological, 370
 — — rapid method of, 371
 — — differential, 372
 — epidemiology and endemiology of, 362
 — etiology of, 363
 — — germ of (*see* Comma bacillus)
 — geographical distribution of, 362
 — history of, 362
 — hyperpyrexia in, 369
 — immunity from, 366
 — immunization against, per os, 378
 — incubation period of, 377
 — inoculation against, 377
 — lower animals and, 365
 — mortality of, 370
 — nursing precautions in, 376
 — pathology of, 366
 — "premonitory diarrhœa" in, 367
 — prophylaxis of, personal, 378
 — quarantine prevention of, 376
 — reaction stage of, 369
 — recognition of organisms post mortem in, 874
 — sequelæ of, 369
 — sicca, 369
 — symptoms of, 367
 — treatment of, 372
 — Cox's, 375
 — essential oils in, 373
 — kaolin in, 373
 — Rogers's, 374
 — subsidiary measures in, 373
 — typhoid, 369
 Choleraic dysentery, 387
 — form of subtertian malaria, 41
 Chromatin of protozoan cells, 672
 Chromatoid bodies, 404
Chrysomya bezziana, 617, 830
 — macellaria, 617
Chrysops dimidiata, 569, 784, 822
 — discalis, 822
 — and tularemia, 264, 265
 — silacea, 570, 784, 822
 Chvostek's sign in pellagra, 355
 Chylous diarrhœa, 558
 — dropsy, 558
 — urine, 557
 Chyluria, 556
 — symptoms of, 556
 — treatment of, 558
 Cilia of protozoa, 673
Cimex boueti, 686
 — hemiptera (rotundatus), 686, 836
 — hirudinis, 686
 — lectularius, 265, 686, 836
 — rotundatus, 686
 Cimicidæ, 836
Cinchona febrifuge in malaria, 75
 — lancifolia, 69
 — ledgeriana, 69
 — pitayensis, 69
 — succirubra, 69
 Cirrhosis, hepatic, and splenomegaly, in Northern Nyasaland, 525
 — infantile biliary, 463
Citellus beecheyi, 246
 — citellus, 245
 — columbianus, 225
 — grammurus beecheyi, 265
 — mugozaricus, 245
 Climatic bubo, 659
 Clonorchiasis, 584
 — diagnosis of, 586
 — etiology of, 585

- Clonorchiasis, geographical distribution of, 584
 ——— pathology of, 585
 ——— prophylaxis of, 586
 ——— treatment of, 586
 Clonorchis sinensis, 585, 713, 716
 ——— characters of, 716
 ——— eggs of, in faeces, 875, and Pl. xxxv, facing p. 874
 ——— habitat of, 716
 ——— life-history of, 717
 ——— pathogenicity of, 585
 Clupida longiceps, 614
 Clupidae, 614
 Cobra, king, 849
 ——— spectacled, 849
 Cobras, 609, 848, 849
 Coccidia, 696
 ——— occurring in man, 697
 Coccidium, life-cycle of, 696
 Cochlomyia macellaria, 617, 618
 Coelogenys subniger, 839
 Cœnurus cerebialis, 750
 ——— glomeratus, 750
 Coko, 486
 Colitis, dysentery and, 439
 Colubridæ, 847
 Colubrine snakes, 609
 Coma in malaria, 39
 Comma bacillus, 363
 ——— causal relation of, to cholera, 365
 ——— cultivation of, 364
 ——— identification of, 371
 ——— immunity and, 366
 ——— toxins of, 365
 Complement-deviation in blastomycosis, 644
 ——— in malaria, 64
 ——— in paragonimiasis, 584
 ——— in schistosomiasis, Eastern, 533
 ——— intestinal, 526
 ——— of bladder, 518
 ——— in typhus fever, 223
 Congo floor-maggot, 804, 828
 Connective tissue in faeces, 879
 Conorhinus (see Triatoma)
 Constipation, post-dysenteric, treatment of, 400
 Continued malarial fever, definition of, 32
 Convulsive seizures in malaria, 40
 "Copra itch," 793
 Coprozoic protozoa, 692
 Coral snakes, 849, 853
 Cordylobia, 804
 ——— anthropophaga, 618, 620, 831
 Corethrinæ, 810
 Cover-slips, cleaning of, 857
 Cox's treatment of cholera, 375
 "Crab yaws," 493
 Crab-louse, 834
 Craw-craw, 631
 Creeping eruption, 619
 "Crescent bodies," 13, 27, 28
 Cricetulus frumentarius, 137
 ——— griseus, 135, 137
 Cristispira balbianii, 708
 ——— genus, 708
 Crithidia, 691
 ——— melophagia, 688
 Crocidura stamplii, 247
 Crotalinæ, 855
 ——— American, synopsis of, 855
 ——— Indo-Australasian, synopsis of, 855
 Crotalus, 855
 ——— bites of, 611
 Crustacea, 792
 Cryptococcus capsulatus, 643
 ——— farciminosus, 643
 ——— linguæpilosæ, 642
 Ctenocephalus canis, 248, 750
 ——— felis, 248
 Ctenopsylla musculi, 248
 Culex, 814
 ——— ægypti, 815
 ——— fatigans, 807, 812, 814
 ——— and dengue, 206
 ——— and Filaria bancrofti, 539, 542, 774, 776
 ——— and plasmodia, 699
 ——— pipiens, 542, 776, 814
 ——— and Filaria bancrofti, 814
 ——— quinquefasciatus (see Culex fatigans)
 ——— skusei, 814
 Culicidæ, 803, 804
 ——— subfamilies of, 810
 ——— (see also Mosquitoes)
 Culicinae, 810
 Culicoides, 821
 ——— and pellagra, 349
 ——— austeni, 785
 Culture media, Adler's, 864
 ——— Boeck and Drbohlav's, 865
 ——— N.N.N., 864
 ——— Noguchi-Wenyon, 864
 Curare, 605
 Cutaneous leishmaniasis, 151
 Cutis anserina in malarial fever, 30
 Cyclophyllidea, 744
 ——— adult, occurring in man, 745
 ——— anatomy of, 744
 ——— eggs of, 745
 ——— larval forms of, in man, 750
 Cyclops bicuspidatus, 790
 ——— leuckarti, 742
 ——— quadricornis, 575, 790
 ——— strenuus, 741, 790
 ——— viridis, 790
 Cynocephalus, 683
 Cyprinus carpis, 718
 Cysticeroid, 748
 Cysticercus bovis, 750
 ——— cellulosæ, 746, 750
 Cystine agar, composition of, 265
 Cyst-passers (Entamoeba histolytica), 405
 ——— incidence of, 406
 Cysts, protozoal, concentration of in faeces, 881
 Cyto-diagnosis, 390, 868
 Cytosome, 673

D

- Daboia, 610
 Dandy fever, 205
 Danysz's bacillus, 260
 Dark-ground illumination, technique of, 883
 Dasypsecta and leishmaniasis americana, 160
 Dasypus sexcinctus, 131, 686
 ——— uncinatus, 131, 686
 Datura, 605
 Davainea asiatica, 750
 ——— formosana, 750
 ——— genus, 750
 ——— madagascariensis, 750
 Davaineidæ, 745
 Death fish, 614
 Deer-fly fever, 264
 Definitive host, 670
 Delhi boil, 151
 Delirium in malaria, sudden, 40
 Demodex folliculorum var. hominis, 796
 Demodicidæ, 792

- Dendraspis*, 850
Dengue, 205
 ——— diagnosis of, 209, 313
 ——— epidemiology and endemiology of, 205
 ——— eruption in, 208
 ——— etiology of, 206
 ——— mosquito and, 206
 ——— geographical distribution of, 205
 ——— incubation period of, 206
 ——— mode of spread of, 205
 ——— mortality of, 209
 ——— pathology of, 206
 ——— prophylaxis of, 210
 ——— rash of, 208, 317
 ——— relapses in, 209
 ——— rheumatoid pains in, 208
 ——— stage of invasion of, 206
 ——— of remission of, 207
 ——— symptoms of, 206
 ——— terminal fever and eruption of, 207
 ——— treatment of, 209
 ——— variability of epidemic type of, 209
Denisonia, 852
Dermacentor andersoni, 225, 799
 ——— *maturatus*, 226
 ——— *occidentalis*, 225 (footnote)
 ——— *reticulatus*, 225 (footnote)
 ——— *venustus*, 799, 800
 ——— and spotted fever of Rocky Mountains, 225, 226, 228
 ——— and tick paralysis, 226 (footnote)
Dermacentroxenus rickettsi, 225, 227
Dermatitis, *ancylostome*, 601
 ——— *linearis migrans*, 619
 ——— *nodular*, 631
 ——— *ulcerating*, 631
Dermatobia, 804
 ——— *cyaniventris*, 617, 620, 833
Dermatophylus, 655
Dermatosis, *acarine*, 658
Derrengadera, 126
Desert sore, 627
Desmodillus auricularis, 246
Detritus in fæces, 879
Dhobie's itch, 644
 ——— diagnosis of, 645
 ——— etiology and nomenclature of, 644
 ——— prophylaxis of, 646
 ——— symptoms of, 645
 ——— treatment of, 645
 Diagnosis of fevers in tropics (*see* Fevers in tropics, diagnosis of)
Diampiphidia locusta, 604
Diaptomus gracilis, 741
Diarrhoea, *hill*, 459
 ——— in diagnosis of fevers in tropics, 320
 ——— premonitory, 367
Dibothriocephalus latus, 601, 740
 ——— characters of, 740
 ——— eggs of, in fæces, 876, and Pl. xxxv, facing p. 874
 ——— geographical distribution of, 740
 ——— habitat of, 740
 ——— life-history and pathogenesis of, 740
 ——— *mansoni*, 742
 ——— geographical distribution of, 742
 ——— ocular sparganosis and, 743
 ——— pathogenesis of, 743
 ——— *lanceatum*, 722
Diemenia, 851
Dientamœba fragilis, 403, 680
Digenæa, 711
 Dilution of serum, progressive, in agglutination test, 368
Dinopsyllus lypus, 246
Diocetophyme renale, 756 (footnote)
Diplogonoporus, 742
 ——— *brauni*, 742
 ——— *grandis*, 742
Diptera, *brachycerous*, 821
 ——— groups of, of medical interest, 803
Dipylidium caninum, 749, 839
 ——— characters of, 749
 ——— eggs of, 750 (fig.)
 ——— geographical distribution of, 749
Dirofilaria immitis, 756
 ——— *inagalhæsi*, 756
Discomyces bovis, 638
 ——— *maduræ*, 638
 ——— *tenuis*, 654
Distira, 849 (footnote)
Distomum ringieri, 581
Divicine, 606
Dog, and *kala-azar*, 135, 150
 ——— "disease," 210
Doliophis, 851
Dracontiasis (*see* Guinea-worm infection)
Dracunculidæ, 756
Dracunculus medinensis, 574, 788
 ——— characters of, 575, 789
 ——— embryo of, 790
 ——— geographical distribution of, 574, 788
 ——— habitat of, 788
 ——— life-history of, 575, 790
 ——— mode of infection with, 575
Dreyer's drop method, 369
Dreysena polymorpha, 718
Dropsy, epidemic, 343
 "Dry beriberi," 329
Dube, 436
 "Dumas," 493
Dum-dum fever, 132
 "Durango," 614
 "Dutch-wife," 634
Dysenteric form of subtertian malaria, 41
 ——— rheumatism, 388
Dysenteries, differential diagnosis of, 437
Dysentery, *amœbic*, 402
 ——— complications of, 410 (*See also* Abscess of brain, *amœbic*; Abscess of epididymis, *amœbic*; Abscess of spleen, *amœbic*; Liver abscess; Pulmonary *amœbiasis*)
 ——— cyst-passers in, 405
 ——— diagnosis of, 411
 ——— from bacillary dysentery, 393
 ——— sigmoidoscopic, 412
 ——— X-rays in, 413
 ——— diet in, 419
 ——— epidemiology of, 402
 ——— etiology of, 402 (*see also* *Entamœba histolytica*)
 ——— geographical distribution of, 402
 ——— hepatitis in, 410
 ——— treatment of, 418
 ——— histology of, 407
 ——— incubation period of, 408
 ——— liver abscess and, 420
 ——— pathology of, 406
 ——— perforation of ulcer in, 418
 ——— prophylaxis of, 419
 ——— superimposed on bacillary dysentery, 410
 ——— symptoms of, 408
 ——— treatment of, 413
 ——— by auremetine, 416
 ——— by bismuth nitrate, 418
 ——— by emetine, 413

Dysentery, amœbic, treatment of, by
 ————— ipecacuanha, 413
 ————— by neosalvarsan, 416
 ————— by rivanol, 418
 ————— by stovarsol, 417
 ————— by yatren, 417
 ————— by yatren and emetine-
 ————— bismuth-iodide com-
 ————— bined, 418
 — and Chilomastix mesnili, 438
 — and colitis, 439
 — and giardia enteritis, 437
 — and internal piles, 439
 — and simple polypus, 439
 — and Trichomonomonas intestinalis, 438
 — and tuberculous ulceration of in-
 ————— testine, 439
 ————— bacillary, 380
 ————— acute, 386
 ————— ascites as a sequel to, 388
 ————— carriers of, 390
 ————— choleraic, 387
 ————— chronic, 387
 ————— treatment of, 398
 ————— surgical, 399
 ————— collapse in, treatment of, 398
 ————— complications of, 388
 ————— treatment of, 398
 ————— contagion in, 381
 ————— cyto-diagnosis of, 390
 ————— diagnosis of, 390
 ————— by examination of stools,
 ————— 390
 ————— cutaneous reaction in, 391
 ————— from amœbiasis, 393
 ————— serological, 392
 ————— sigmoidoscopic, 393
 ————— epidemiology of, 381
 ————— etiology of, 382
 ————— predisposing causes, 388
 ————— food and clothing in, 401
 ————— fulminating, 386
 ————— geographical distribution of
 ————— 381
 ————— germs of (see *Bacillus dysen-*
 ————— *teriae*)
 ————— histopathology of, 385
 ————— houseflies as carriers of, 381
 ————— incubation period of, 384
 ————— mild or catarrhal forms of,
 ————— 386
 ————— pathology of, 384
 ————— prognosis of, 394
 ————— prophylaxis of, 401
 ————— by inoculation, 401
 ————— relapsing, 387
 ————— stools in, 385
 ————— symptoms of, 385
 ————— treatment of, 394
 ————— by rectal irrigation, 398
 ————— by serum, 396
 ————— surgical, 399
 ————— water as medium of infection
 ————— in, 382
 ————— balantidial, 436
 ————— bilharzial, 436
 ————— due to *Gesphagostomum apiosto-*
 ————— *mum*, 437
 ————— followed by sprue, 447
 ————— forms of, not mutually exclusive,
 ————— 380
 ————— helminthic, 436
 ————— isolation of organisms post mortem
 ————— in, 874
 ————— kala-azar, 439
 ————— malarial, 438
 ————— mixed infections in, 437
 ————— relation of liver abscess to, 420
 ————— spirochaetal, 438
 ————— types of, 380

E

"East Coast fever," 704
 Eastern schistosomiasis, 530
 E.B.I., in amœbic dysentery, 413
 — in liver abscess, 430
 Echinococcus granulosus, 744, 750
 ————— characters of, 750
 ————— diagnosis of, 752
 ————— habitat of, 750
 ————— larval forms of, 750
 ————— life-history and pathogenesis
 ————— of, 753
 Echinostomum ilocanum, 722
 ————— malayanum, 722
 Echis, 854, 855
 ————— carinatus, 611
 Eckujin, 604
 Ectoplasm, 673
 Ectosarc, 673
 Eggs of *Ancylostoma duodenale*, 591,
 ————— 596, 760, 876, and Pl. xxxv, 14,
 ————— facing p. 874
 — of *Ascaris lumbricoides*, 587, 875,
 — and Pl. xxxv, 7, 8, 9, 10, facing
 — p. 874
 — of *Clonorchis sinensis*, 585, 717, 875,
 — and Pl. xxxv, 5, facing p. 874
 — of *Demodex folliculorum* var. *homi-*
 — *nis*, 795
 — of *Dibothriocephalus latus*, 740, 876,
 — and Pl. xxxv, 21, facing p. 874
 — of *Dipylidium caninum*, 750
 — of *Echinococcus granulosus*, 751
 — of *Enterobius vermicularis*, 767, 875,
 — and Pl. xxxv, 19, facing p. 874
 — of *Fasciola hepatica*, 714, 875
 — of *Fasciolopsis buskii*, 715, 875, and
 — Pl. xxxv, 1, facing p. 874
 — of *Gastrodiscoides hominis*, 734
 — of helminths, preservation of, 885
 — of *Heterodera radiclecola*, 876, and
 — Pl. xxxv, 22, facing p. 874
 — of *Heterophyes heterophyes*, 719,
 — 875, and Pl. xxxv, 3, facing
 — p. 874
 — of *Hymenolepis diminuta*, 749
 — — *nana*, 748, 876, and Pl. xxxv,
 — 20, facing p. 874
 — of intestinal parasites, examination
 — of læces for, 875
 — — method of concentrating,
 — 876
 — of *Linguatula serrata*, 801
 — of *Loxotrema ovatum*, 719, and
 — Pl. xxxv, 6, facing p. 874
 — of mosquitoes, 804
 — of *Necator americanus*, 595, 761,
 — and Pl. xxxv, 15, facing p.
 — 874
 — of *Gesphagostomum apiostomum*,
 — 762
 — of *Opisthorchis felinus*, 717 and
 — Pl. xxxv, 4, facing p. 874
 — of *Paragonimus ringeri*, 584, 720,
 — and Pl. xxxv, 2, facing p. 874
 — of *Phlebotomus papatasi*, 818, 819
 — of *Physaloptera mordens*, 759
 — of *Porocephalus armillatus*, 802
 — of *Schistosoma hamatobium*, 724,
 — 731, 875, and Pl. xxxv, 11,
 — facing p. 874
 — — *japonicum*, 730, 731, 875, and
 — Pl. xxxv, 13, facing p. 874
 — — *mansoni*, 728, 731, 526, 875,
 — and Pl. xxxv, 12, facing p.
 — 874
 — of schistosomes, detection of, in
 — læces, Fülleborn's method for, 77

- Eggs of *Simulium*, 821
 of *Strongyloides stercoralis*, 765
 of *Tænia saginata*, 747, 876, and Pl. xxxv, 17, facing p. 874
 solium, 746, 876, and Pl. xxxv, 16, facing p. 874
 of *Ternidens deminutus*, 764
 of *Trichinella spiralis*, 770
 of *Trichuris trichiura*, 875, and Pl. xxxv, 18, facing p. 874
 Egyptian chlorosis, 589
 splenomegaly (see *Schistosomiasis*, visceral)
Eimeria, 697, 698
 clupearum, 698
 oxyspora, 698
 sardinae, 698
 schubergi, 696
 wenyoni, 698
Elapechis, 850
Elaphe climacophora, 742
Elapinae, 849, 850
 genera of, African, 850
 American, 853
 Asiatic, 850
 Australian, 851
 synopsis of, 850
Elapognathus, 853
Elaps, 849, 850, 853
Elephantiasis, 560
 a filarial disease, 547
 græcorum, 465
 of arms, 566
 of legs, 561
 treatment of, 562
 Kondoleon's operation, 563
 Lanz's operation, 563
 medicinal, 563
 of limited skin areas, 566
 of scrotum, 563
 treatment of, 564
 operative, 564
 of vulva and mammae, 566
 pathology of, 547
 recurring erysipelatoid attacks in, 561
Elephantoid fever, 551
Embodomonas intestinalis, 692, 693, 865
Embryophore, 745
Emetine in amœbic dysentery, 413
 in oriental sore, 159
 in paragonimiasis, 584
 in schistosomiasis, 521, 527, 534
Emetine - bismuth - iodide in amœbic dysentery, 414
 in liver abscess, 430
Emetine-periodide in amœbic dysentery, 416
Emydocephalus, 848
 Encystment in liver abscess, 422
Endamœba dysenteriae (see *Entamœba histolytica*)
Endemic funiculitis, 559
 hæmaturia, 511
 hæmoptysis (see *Paragonimiasis*)
 hypertrophy of os calcis, 663
Endodermophyton concentricum, 648
 indicum, 648
Endolimax nana, 403, 678
Enhydrina, 849
 schistosa, 848
Entamœba coli, 403, 676, 678
 cysts of, 677
 in bacillary-dysentery exudate, 391
 incidence of, 677
 life-history of, 677
 dysenteriae (see *Entamœba histolytica*)
 gingivalis, 677
Entamœba histolytica, 402, 674, 678
 culture of, 675
 cyst-passers, 405
 incidence of, 406
 cysts of, 404, 674
 concentration of, in faeces, 881
 detection of, in stools, 403
 life-history of, 404
 non-pathogenic species of, 403
 tetragena (see *Entamœba histolytica*)
Entamœbæ, discovery of, in stools, 402
 in liver abscess, 422
Enteric fevers, 282
 agglutination in, methods of, 868
 atropine test in, 292
 bacteriology of, post-mortem, 285
 carriers of, 283
 detection of, 291
 culture of excreta in, 291
 cystitis in, 298
 diagnosis of, 314
 bacteriological, 291
 by diazo reaction, 292
 by Marris's atropine test, 292
 by Russo's methylene-blue test, 292
 clinical, 287, 290
 differential, 292
 from appendicitis, 293
 from *Bacillus coli* infections, 293
 from typhus, 293
 typhoid from paratyphoid, 293
 in inoculated persons, 873
 of malaria from, 67
 of rash of, 318
 serological, 291
 in inoculated persons, 292
 epidemiology and endemiology of, 283
 etiology of, 284
 organisms of, 284
 geographical distribution of, 282
 hæmoculture in, 291
 history of, 282
 incubation period of, 285
 inoculation against, 294
 isolation of organisms post-mortem in, 874
 onset of, 285
 pathology of, 285
 "period of expectation" in, 292
 post-mortem appearances in, 285
 bacteriology of, 284, 874
 preparation of vaccines against, 295
 prevalence of, 282
 prophylaxis of, 295
 measures to avoid infection, 296
 triple vaccine in, 295
 preparation of, 295
 statistics of results, 295
 pulse-temperature ratio in, 289
 pyelitis in, 298
 pyrexia in, 288
 rose spots in, 290
 splenic enlargement in, 29

- Enteric fevers, symptoms of, 285
 ———— toxæmia in, 289
 ———— treatment of, 294
 ———— by vaccine, 294
 ———— Widal reaction in, 291
 Enteric-like fevers, 296
 ———— due to *B. coli* infections, 297
 ———— due to *B. fecalis alkaligenes*,
 etc., 296
 Enterobius vermicularis, 756, 767
 ———— characters of, 767
 ———— eggs of, in fæces, 875, and
 Pl. xxxv
 ———— habitat of, 767
 ———— life-history and pathogenesis
 of, 767
 ———— treatment, 768
 Entero-colitis, acute, sprue secondary
 to, 447
 Entomology, medical, 792
 Eosinophiles, 861
 Eparseno, 163
 Ephredine, 482
 E.P.I., in amoebic dysentery, 416
 Epidemic dropsy, 343
 ———— dysentery (see Dysentery, bacillary)
 Epidermophyton inguinale, 645, 646, 647
 Epididymis, amoebic abscess of, 435
 Erathyrus, 837, 838
 ———— and South American trypanosomes,
 128
 ———— cuspidatus, 686, 838
 Erinaceus æthiopicus, 801
 Eriocheir japonicum, 721, 722
 ———— sinensis, 721
 Eruptions of fevers in tropics, diagnosis
 of, 317
 Erythroblasts, 862
 Erythrocytes, 862
 Erythrophloeum guineense, 604
 Esanofele, 75
 Esanofelina, 75
 Esox lucius, 742
 Espundia, 160
 Euchinine in malaria, 73
 Euphorbia candelabrum, 604
 Enquinine in malaria, 73
 Euscorpius italicus, 614
 Eustrongylus visceralis, 756
 Exanthematous glandular fever, 228
 Exudates, pathological, spectroscopic
 examination of, 882
 Eye complications in bacillary dysentery,
 389, 398

F

- Fæces, examination of, chemical, 874
 ———— for comma bacillus, 371
 ———— microscopic, for eggs of intes-
 tinal parasites, 874
 ———— for elements other than
 eggs, 879
 ———— spectroscopic, 882
 ———— organisms from, recognition of, by
 agglutination, 874
 Faget's sign, 197
 Fahrenheit and Centigrade scales, rela-
 tion between, 889
 Fairley's reaction, 518
 Famine dropsy, 343
 ———— fever, 164
 Fannia canicularis, 620, 82
 ———— scalaris, 621
 Fasciola gigantica, 714
 ———— hepatica, 714
 ———— eggs of, 714
 ———— in fæces, 875

- Fasciolidæ, 713,
 Fasciolopsis buskii, 713, 715
 ———— characters of, 715
 ———— eggs of, in fæces, 875, and
 Pl. xxxv, 1, facing p. 874
 ———— geographical distribution of,
 715
 ———— habitat of, 715
 ———— life-history of, 715
 ———— pathogenesis and treatment,
 716
 Fats in fæces, 879
 Fatty acids in fæces, 879
 Febris recurrens, 164
 ———— undulans, 269
 Feet, ringworm of, 646
 Fever, simple continued, 188
 Fevers in tropics, diagnosis of, 309
 ———— dengue, 313
 ———— enteric, 314
 ———— filarial, 316
 ———— helminthic, 316
 ———— infectious jaundice, 313
 ———— kala-azar, 312
 ———— liver abscess, 315
 ———— malarial, 309
 ———— phlebotomus, 313
 ———— relapsing, 311
 ———— seven-day, 313
 ———— trypanosomiasis, 312
 ———— typhus, 315
 ———— undulant, 314
 ———— yellow, 313
 Fiebre amarilla, 190
 Field-vole, and seven-day fever, 188
 Fièvre buttoneuse, 222
 Filaria bancrofti, 535, 536, 756, 772
 ———— characters of, 536, 772
 ———— chitinization of, in mosquito,
 544
 ———— cretification of, in man, 550
 ———— discovery of, 535
 ———— embryo of, 772
 ———— female, 772
 ———— geographical distribution of,
 536, 772
 ———— habitat of, 772
 ———— host of, definitive, 544, 670
 ———— intermediary, 542
 ———— life-history of, 775
 ———— male, 772
 ———— microfilarie (see Micro-
 filaria bancrofti)
 ———— parent forms of, 536
 ———— transference of, to human
 host, 544
 ———— transmission of, 670, 814
 ———— conjunctivæ, 756½
 ———— demarquay, 779
 ———— malayi, 779
 ———— martis, 772 (footnote)
 ———— nocturna, 535
 ———— ozzardi, 756, 779
 ———— characters of, 779
 ———— sanguinis hominis, 535
 ———— volvulus, 572
 (see also Microfilaria)
 Filariæ, metamorphosis of, in mosquito,
 542
 Filarial diseases due to Filaria ban-
 crofti, abscess, 550
 ———— chylous dropsy and
 diarrhoea, 558
 ———— chyluria, 557
 ———— elephantiasis (see
 Elephantiasis)
 ———— enumeration of, 549
 ———— glandular enlarge-
 ment, 553
 ———— lymph scrotum, 554

- Filarial diseases due to *Filaria***
 lymphangitis and elephantoid fever, 550
 ——— lymphatic varices, 553
 ——— lymphuria, 557
 ——— orchitis, endemic funiculitis, and hydrocele, 559
 ——— synovitis, 559
 ——— thickened lymphatic trunks, 553
 ——— varicose groin-glands, 551
 ——— embryos, films for demonstration of, 859
 ——— fever, diagnosis of, 316
 ——— non-periodicity, 541
 ——— periodicity, 538
Filariasis, 535, 569
 ——— definition of, 535
 ——— due to *F. bancrofti*, 536
 ——— epidemiology and endemology of, 544
 ——— etiology of, 536
 ——— geographical distribution and prevalence of, 536
 ——— lymphatic varix, pathology of, 546
 ——— pathology of, 544, 547
 ——— prophylaxis of, 568
 ——— treatment of, 566
 ——— (see also *Filaria* diseases due to *Filaria bancrofti*)
 ——— due to *Loa loa*, 569
 ——— etiology of, 569
 ——— geographical distribution of, 569
 ——— history of, 569
 ——— pathology of, 570
 ——— symptoms of, 571
 ——— history of, 535
 ——— originating in injury of lymphatic systems, 545
 ——— parasites of, nomenclature of, 535
 ——— pathological importance of, 535
Filariidæ, 756
Films, blood- (see *Blood-films*)
 ——— for demonstration of protozoa in faeces, 882
 ——— stained, detection of spirochaetes by, 885
Finlaya togol, and *Filaria bancrofti*, 776
Fishes, poisonous, 613
Fish-poisoning, 614
"Flagellar" and **"aflagellar,"** use of, 681 (footnote)
Flagellata, 680
"Flagellated body" in malaria, 12, 13
 ——— method of staining of, 860
Flagellates, blood (see *Hæmoflagellata*)
 ——— intestinal, 692
 ——— types of, 690
Flagellum of malaria parasite, 12
 ——— of protozoa, 672
Flea, and plague, 247
 ——— rat- (see *Rat-flea*)
Fleas, characters of, 839
 ——— disinfection and, 841
Flesh-flies, 804, 827
Flexner's bacillus, 380, 383
Flies (see *Musca domestica*; *Muscidæ*; *Muscoid flies*)
Floatation method of concentrating helminth eggs, 876
Flood fever (see *Japanese river fever*)
"Floor maggot," 620
"Fly disease of Africa," 686
Fontana's staining method, 885
Food-deficiency theory of beriberi, 323
 ——— of pellagra, 350
Foods, poisonous, 606
Foot, mossy, 641
 ——— yaws, 493
Forest yaws, 160
Fowls, and beriberi, 323
Framboesia (see *Yaws*)
Fruit treatment of sprue, 452
Fülleborn's method of detecting schisto-
 some eggs in faeces, 877
Fungous skin diseases, 632
Funiculitis, endemic, 559
Furina, 851
Furunculosis, 630
- G**
- "Gadflies,"** 803, 821
Gall-bladder in blackwater fever, 62
Gambiense sleeping sickness (see *Sleeping sickness, gambiense*)
Gametocyte, 700
Gametocytes of malarial parasites, 12 13
 23, 24, 700
Gametogony, 24, 26, 29, 700
Ganga, 608
Gangosa, 495
Garrow's agglutinator, 870
Gastric form of malarial fever, 40
Gastrodiscoides hominis, 733
 ——— characters of, 733
 ——— geographical distribution of, 733
 ——— habitat of, 733
 ——— pathogenesis of, and treatment, 734
Gastrophilus hæmorrhoidalis, 619
 ——— veterinus, 619
General diseases of undetermined nature, 321
 ——— paralysis of insane, malaria injections for, 32
Geosciurus capensis, 246
Germanin (see "*Bayer 205*")
"Giardia enteritis," and dysentery, 437
 ——— genus, 695
 ——— intestinalis, 437, 695
 ——— lamblia, 695
Gibson, Graeme, and inoculation against bacillary dysentery, 401
Giemsa's stain, 859
 ——— staining methods, 885
Gigantorhynchus gigas, 791
 ——— moniliformis, 791
Glandular enlargement, and filarial disease, 553
 ——— in diagnosis of fevers in tropics, 319
Glauconiidæ, 846
"Globi" of leprosy, 469
Gloriosa superba, 605
Glossina, 804
 ——— austeni, table facing p. 824
 ——— distribution of, 824
 ——— brevipalpis, 686, 824, and table facing p. 824
 ——— distribution of, 823, 824
 ——— group, characters of, table facing p. 824
 ——— caliginea, 824, and table facing p. 824
 ——— distribution of, 824
 ——— characters of, 823
 ——— fusca, 823, 825, and table facing p. 824

Glossina fusca, distribution of, 823
 ——— group, characters of, table facing p. 824
 ——— fuscipleuris, table facing p. 824
 ——— longipalpis, 687, and table facing p. 824
 ——— distribution of, 824
 ——— longipennis, table facing p. 824
 ——— distribution of, 824
 ——— medicorum, table facing p. 824
 ——— morstans, 103, 121, 123, 124, 684, 687, 823, 824, 825, and table facing p. 824
 ——— distribution of, 823, 824
 ——— group, characters of, table facing p. 824
 ——— nigrofusca, table facing p. 824
 ——— pallicera, table facing p. 824
 ——— distribution of, 824
 ——— pallidipes, 686, 824, and table facing p. 824
 ——— distribution of, 824
 ——— palpalis, 101, 103, 104, 121, 123, 124, 683, 684, 687, 824, and table facing p. 824
 ——— distribution of, 723, 724
 ——— group, characters of, table facing p. 824
 ——— schwetzi, table facing p. 824
 ——— severini, table facing p. 824
 ——— swynnertoni, 125, 684, 824, and table facing p. 824
 ——— distribution of, 824
 ——— tabaniformis, table facing p. 824
 ——— tachinoides, 686, 824, and table facing p. 824
 ——— distribution of, 824
Glossinæ, 804, 823
 ——— Austen's classification of, table facing p. 824
 ——— development of trypanosomes in, 683, 684, 686
 ——— distribution of, 823
 ——— habits of, 825
 ——— Newstead's classification of, 823 (footnote)
 ——— reproduction of, 825
 ——— resting attitude of, 823
 ——— role of, in trypanosomiasis, 103
Glycophagus, 658
Glyphodon, 851
Glyptocranium gasteracanthoides, 615
Gnathostoma spinigerum, 756
 Goats and undulant fever, 281
 Goundou, 496
 ——— and yaws, relation between, 497
 Gower's hæmoglobinometer, 863
 Grahamella, 704
 "Grain itch," 658
 Granules, starch, in fæces, 879
Granuloma inguinale, 505
 ——— venereum, 505
 Griesinger's disease, 181
 "Grocer's itch," 658, 793
 "Gros nez," 496
 Ground itch, 601
 Ground-squirrel, 225
 ——— of California, and plague, 246
Guinea-worm infection, 574
 ——— diagnosis of, 579
 ——— etiology of, 575
 ——— geographical distribution of, 574
 ——— mode of, 575
 ——— parasite of (*see Dracunculus medinensis*)
 ——— pathology and symptoms of, 576
 ——— prophylaxis of, 580
 ——— treatment of, 579

H

Habronema muscæ, 827
Hæmadipsa cinnabarina, 226 (footnote)
 ——— leachi, 797
 ——— zeylanica, 621
Hæmatobia, 823
 ——— auctt, 823
 ——— stimulans, 826
Hæmatopota, 821, 822
Hæmatoxylin and eosin stain, 860
 ——— test, Tribondeau's, for reaction of distilled water, 861
Hæmaturia, endemic, 511
Hæmaturic fever (*see* Blackwater fever)
 "Hæmoclastic shock"
Hæmoculture in diagnosis of enteric fever, 291
 ——— of undulant fever, 273
Hæmocystidium, 699
Hæmodipsus ventricosus, 265
Hæmoflagellata, 681
 ——— nomenclature of, 690
Hæmofuscin in malaria, 61
Hæmoglobin, estimation of, 863
 ——— spectrum of, 883
Hæmoglobinuria in malaria, 52
 ——— paroxysmal, 44
Hæmoglobinuric fever, 44
Hæmogregarina, 704
 ——— balfouri, 704
 ——— characters of, 704
 ——— stepanowi, 704
 ——— (*see also* Hepatozoon)
Hæmolytic in blackwater fever, 48
 ——— in malaria, 57
Hæmoproteus, 701
 ——— columbæ, 701
Hæmoptysis, endemic (*see* Paragonimiasis)
Hæmorrhages, purpuric, into skin in subtertian malaria, 41
Hæmorrhagic forms of subtertian malaria, 41
Hæmosiderin in malaria, 61
Hæmosporidia, 698
Hæmozoin, 10
 Haffkine's anti-cholera inoculation, 377
 ——— anti-plague inoculations, 261
Halteridium, 701
 "Halzoun," 714
 Hamadryad, 849
 Hamdi's antityphus inoculation, 224
 Harvest-bugs, 794
 Hascheesch, 608
 Hay flame-gun, 92
 Head-shields of snakes, 845
 Heart in malaria, 57, 62
 "Heat apoplexy," malaria and, 39
 Heat-exhaustion, 302
 ——— etiology of, 302
 ——— symptoms of, 302
 ——— treatment of, 303
 Heat-hyperpyrexia, 303
 ——— auto-intoxication in, 304
 ——— choleraic type of, 305
 ——— diagnosis of, 306
 ——— etiology of, 303
 ——— gastric type of, 305
 ——— geographical distribution of, 303
 ——— pathology of, 304
 ——— prophylaxis of, 307
 ——— symptoms of, 304
 ——— treatment of, 306
 ——— true, 305
 Heat-stroke, 302
Helcosoma tropicum, 151
 Helminthic dysentery, 436
 ——— fevers, diagnosis of, 316

Helminthology, medical, 711
 ——— nemathelminthes, 754
 ——— platyhelminthes, 711
 "Helminthoma elastica," 553
 Helminths, eggs of, preservation of, 886
 ——— preservation of, 885
 ——— (see also Eggs)
 Heloderma horridum, 613
 ——— suspectum, 613
 Hemibia, 732
 Hemibungarus, 851
 Hemiptera, 835
 Hemipya abscess (see Liver abscess)
 ——— amoebiasis, 420
 Hepaticola hepatica, 756, 769
 Hepatitis, amoebic, acute, 410
 ——— treatment of, 418
 Hepatozoon, 704
 ——— balfouri, 704, 705
 ——— canis, 704, 705
 ——— muris, 704, 705
 Herpetic eruptions in malarial cachexia, 54
 Herpetology, medical, 844
 Herpetomonas, 692
 Hess's method of diagnosing scurvy, 359
 Heterodera radicola, eggs of, in faeces, 876, and Pl. xxxv, 22, facing p. 874
 Heterophyes heterophyes, 718
 ——— characters of, 718
 ——— eggs of, in faeces, 875, and Pl. xxxv, 3, facing p. 874
 ——— geographical distribution of, 718
 ——— habitat of, 718
 ——— life-history of, 719
 Heterophyidae, 713
 Hexamita, 695
 Hill diarrhoea, 459
 ——— distribution of, 459
 ——— etiology and pathology of, 460
 ——— symptoms of, 460
 ——— treatment of, 460
 Hinton, M. A. C., and plague rats, 262
 Hippobosca, 804
 Homorelaps, 850
 Hongkong foot, 646
 Hookworm (see Ancylostoma)
 ——— disease (see Ancylostomiasis)
 Hoplocephalus, 852
 Horse-leech, 621
 Host, definitive, 670
 ——— intermediate, 670
 Housedfly, 381, 621, 804, 826
 Hung's method for detecting helminth eggs in faeces, 877
 Hyalomma aegyptum, 796
 Hydatid cysts, 752
 ——— alveolar, 753
 ——— multilocular, 753
 ——— unilocular, 753
 ——— (see also Echinococcus granulosus)
 "—— thrill," 752
 Hydnocarpus anthelmintica, 480
 ——— wightiana, 480
 Hydrelaps, 849
 Hydrocele, filarial, 559
 Hydrophiinae, 848
 Hydrophis, 849
 Hymenolepidæ, 745
 Hymenolepis diminuta, 749, 839
 ——— characters of, 749
 ——— geographical distribution of, 749
 ——— habitat of, 749
 ——— life-history of, 749
 ——— fraterna, 747
 ——— longior, 747

Hymenolepis murina, 747
 ——— nana, 602, 747
 ——— characters of, 748
 ——— eggs of, in faeces, 876, and Pl. xxxv, 20, facing p. 874
 ——— geographical distribution of, 748
 ——— habitat of, 747
 ——— pathogenesis of, 748
 ——— treatment, 748
 Hyoscyamine, 605
 Hyoscyamus fahozlez, 606
 Hyperpyrexia, heat- (see Heat-hyperpyrexia)
 ——— in cholera, 369
 ——— in diagnosis of fevers in tropics, 316
 ——— in malaria, 39
 ——— treatment of, 83
 Hypoderma, 619
 Hypsobia, 732

I

Icterus gravis (see Infectious jaundice)
 Idus melanotis, 718
 Ilysiidae, 847
 Imperial and metric standards, relation between, 889
 Indian hemp, 608
 ——— Plague Commission, 248
 ——— tick typhus, 224
 Indiella mansonii, 639
 ——— reynieri, 640
 ——— somaliensis, 640
 Infantile biliary cirrhosis, 463
 Infectious jaundice, 181
 ——— diagnosis of, 186, 313
 ——— epidemiology and endemiology of, 182
 ——— etiology of, 182
 ——— geographical distribution of, 181
 ——— history of, 181
 ——— incubation period of, 184
 ——— pathology of, 184
 ——— prophylaxis of, 188
 ——— symptoms of, 184
 ——— treatment of, 187
 Infective granulomatous diseases, 465
 Infusoria, 706, 674
 ——— definition of, 674
 Injections, intramuscular, technique of, 666
 ——— intravenous, technique of, 664, 667
 ——— saline, technique of, 667
 Inoculation, prophylactic, in alastrim, 301
 ——— in bacillary dysentery, 401
 ——— in cholera, 377
 ——— in enteric fevers, 295
 ——— in plague, 261
 ——— in relapsing fever, 172
 ——— in typhus fever, 224
 ——— in undulant fever, 281
 ——— in yellow fever, 204
 Insecta, characters of, 792, 803
 ——— diptera, 803
 ——— method of reproduction of, 803
 Insolation, 303
 Intermediate host, 670
 Intermittent malarial fever, definition of, 32
 Intestinal atrophy consequent on sprue, 448
 ——— myiasis, 620
 ——— parasites (see Parasites, intestinal)
 ——— sand in faeces, 881

Intoxication theory of pellagra, 349
 Intramuscular injections, technique of, 666
 Intravenous injections, technique of, 664, 667
 ——— transfusion, technique of, 668
Inuus cynomolgus, 699
 Inversion phenomenon in agglutination, 873
Iodameba bütschlii, 403, 679
 ——— cysts of, 679
 "Iodine" cysts, 679
Iodocin, 481
Ipecacuanha in amoebic dysentery, 413
 ——— (see also Emetine)
Ipob, 604
 Isolation of organisms post mortem, 874
Isospora belli, 697, 698
 ——— *hominis*, 697
Ispaghula in chronic bacillary dysentery, 400
 Itch, prevention and treatment of, 792
 Itch-mite, 792
Ixodes holocylus, 226 (footnote)
 ——— *pilosus*, 226 (footnote)
 ——— *ricinus*, 226, 796
Ixodidae, 792, 795
 ——— life-history of, 796
Ixodinae, 795

J

Janthinosoma lutzi, 834
 Japanese river fever, 228
 ——— diagnosis of, 232
 ——— rash of, 319
 ——— distribution of, 228
 ——— etiology of, 229
 ——— history of, 229
 ——— incubation period of, 231
 ——— intermediary host of virus of, 794
 ——— mortality of, 228, 232
 ——— pathology of, 230
 ——— prophylaxis of, 232
 ——— symptoms of, 230
 ——— treatment of, 232
 Jaundice in diagnosis of fevers in tropics, 319
 ——— infectious (see Infectious jaundice)
Java febrifuge in malaria, 75
 "Jinja" fly, 821
 Jongek test in beriberi, 338
Juxta-articular nodules, 499

K

"K abure," 532
 "Kachang hjau," 326
Kaffir milkpox, 299
Kakke, 321
Kala-azar, 132
 ——— canine, 150, 151
 ——— diagnosis of, 144, 312
 ——— by aldehyde test, 146
 ——— by biochemical reactions, 146
 ——— by splenic puncture, 144
 ——— differential, 146
 ——— from gambiense sleeping sickness, 115
 ——— dysentery, 439
 ——— epidemiology of, 133
 ——— etiology of, 134
 ——— geographical distribution of, 132

Kala-azar, history of, 132
 ——— incubation period of, 139
 ——— infantile, 134, 150
 ——— relation of, to canine form, 150
 ——— mode of transmission of, 135
 ——— parasite of, 134
 ——— pathology of, 139
 ——— predisposing causes of, 139
 ——— prophylaxis of, 150
 ——— relation of, to oriental sore, 151
 ——— symptoms of, 139
 ——— treatment of, 147
 ——— by intramuscular antimony tartrate, 148
 ——— by intravenous antimony-tartrate, 147
 ——— by other antimony compounds, 148
Kaolin in cholera, 373
Karapata disease (see *Carapata* disease)
Karyokinesis, 673
Karyolymph, 672
Karyosome, 672
Katayama, 732
 ——— disease, 536
 "Katipo," 615
Kawa, 608
Kedani mite, 229, 794
 ——— disease, 228
Keloid, 623
 "Kerandel's symptom," 108
Khasari, 606
Kidney in malaria, 59
Kinetoplast, 672
King cobra, 849
 ——— fish, 614
 "Kissing bug," 838
Klebs-Löffler bacillus, and veld sore, 627, 629
 "Koch's blue bodies," 704
Kola tree, 608
Kondoleon's operation for elephantiasis, 563
Kraits, 609, 848, 849
 "Kurchee" bark in amoebic dysentery, 417

L

Laboratory methods in tropical medicine, 857
Lacertilia, 844
Lachesis, 855
 Lacto-reaction in undulant fever, 281
Lagochilascaris minor, 756
Lambia intestinalis, 695
Lamys (see *Triatoma*)
Lane's centrifuge, 876
Lankesteria culicis, 706
Lanz's operation for elephantiasis, 563
Lapemis, 849
Larva migrans, 619
 Larvæ, blood-sucking, 620
 Larvicides for anophelines, 90, 91, 92
Lathyrism, 606
Lathyrus sativus, 606
Laticauda, 848
Latrodectus curacaviensis, 615
 ——— *geometricus*, 615
 ——— *basselti*, 615
 ——— *mactans*, 615
 ——— *tredecimguttatus*, 615
Laveran, and discovery of malaria parasite, 1
Laverania malarie (see *Plasmodium falciparum*)
 Law of priority, 671
Leech infection, 621

- Leishman-Donovan body (*see* *Leishmania donovani*)
- Leishmania*, 132, 688
- *americana*, 689
 - *braziliensis*, 161, 689
 - *donovani*, 132, 156, 688
 - flagellate stage of, on culture, 689
 - in man, 688
 - infantum, 134, 150, 689
 - life-history of, 689
 - myoxi, 152
 - tropica, 151, 689
- Leishmaniasis*, 132
- *americana*, 160
 - diagnosis of, 161
 - distribution of, 160
 - history of, 160
 - symptoms and etiology of, 160
 - treatment of, 162
 - cutaneous, 157
- (*see also* Kala-azar; Oriental sore)
- Leishmanoid*, dermal, 142
- Leishman's stain*, 859
- Lelaps echidninus*, 705
- "Leper juice," 468
- Lepidosis*, 845
- Leproma*, 468, 469
- Leprosy*, 465
- age and, 465
 - anæsthesia in, 475
 - bacillus (*see* *Bacillus lepræ*)
 - climate and, 466
 - contagiousness of, 467
 - diagnosis of, 477
 - epidemiology and endemiology of, 465
 - etiology of, 466
 - galloping, 480
 - geographical distribution of, 465
 - heredity and, 466
 - history of, 465
 - in rats, 469
 - incubation period of, 470
 - leproma in, 469
 - nerve, 473
 - prognosis of, 479
 - nodular, 472
 - prognosis of, 479
 - occupation and, 466
 - pathology of, 469
 - prognosis of, 479
 - prophylaxis of, 484
 - recent introduction of, into virgin soil, 465
 - segregation in, 484
 - sex and, 466
 - social and hygienic conditions and, 466
 - stages of, 470
 - incubation period, 470
 - primary exanthem, 471
 - infection, 470
 - prodromata, 471
 - specific deposit, 472
 - symptoms of, 470
 - transmission of, 466
 - treatment of, 480
 - by Alepole, 482
 - by antimony, 482
 - by carbon-dioxide snow, 482
 - by chaulmoogra oil, 480
 - by hydnocarpus oil, 480, 481
 - by operation, 483
 - by potassium iodide, 482
 - by protein-shock therapy, 483
 - by sodium gynocardate, 481
 - by sodium hydnocarpate, 482
 - by sodium morrhuate, 482
 - hygienic, 480
 - surgical, 483
- Leprosy*, uninoculability of, 466
- white, diagnosis of leprosy from, 478
- Leptocimex boueti*, 836
- Leptoconops*, 821
- Leptomonas*, 153, 689, 691
- ctenocephali, 689, 691
- Leptospira* genus, 710
- hebdomadis, 188, 189, 710
 - and seven-day fever, 188
 - icterohæmorrhagicæ, 181, 182, 183, 184 187, 189, 190, 193, 709, 710, 865, 885
 - and infectious jaundice, 181
 - icteroides, 182, 187, 190, 193, 710
 - and yellow fever, 190
 - animal experiments with, 193
 - transmission of, through mosquito, 193
 - pyrogenes, 189
- Leptospiræ*, and febrile conditions in Sumatra, 189
- Leptospirosis*, 181
- (*see also* Infectious Jaundice; Seven Day Fever)
- Leptotrombicula*, 794
- Leptus autumnalis*, 794
- Leucocytes* in childhood, 862
- in malaria, 58
 - varieties of, 861
- Leucocytosis*, 861
- Leucocytozoon*, 702
- neavi, 703
 - ziemanni, 703
- Leucoderma*, 623
- diagnosis of leprosy from, 478
- Leucogobio guntheri*, 717
- Leucopenia*, 861
- Lice*, 834
- and relapsing fever, 164, 168, 170
 - and typhus fever, 219
- Lichen tropicus*, 632
- Limnæa amygdalum*, 714, 736
- natalensis, 727, 731
 - truncatula, 714
- Limnatis nilotica*, 621
- Limnotragus spekei*, 104, 105, 684, 687
- Lingua nigra*, 642
- Linguatula serrata*, 801, 802
- Linguatulidæ*, characters of, 799
- Linin*, 672
- Lithobius forficatus*, 696
- Liver abscess*, 420
- adhesions in, 421
 - area of dullness in, 425
 - aspiration in, diagnostic, 428
 - preliminary, 429
 - climate and, 420
 - diagnosis of, 427
 - from malaria, 66, 428
 - discharging into serous cavity, treatment of, 434
 - discharging through lung, treatment of, 433
 - drainage of, by aspiration, 430
 - encystment in, 422
 - entamœbæ in, 422
 - etiology of, 420
 - fever, in, 424
 - diagnosis of, 315
 - geographical distribution of, 420
 - intestinal ulceration in, 421
 - mortality of, 426
 - pathology of, 420
 - periodicity of fever in, 424, 427
 - pulmonary inflammation in, 421
 - pus in, characters of, 421
 - pyogenic organisms in, 422

Liver abscess, race, sex and climate in, 420
 ——— relation of, to amœbic dysentery, 420
 ——— rupture of, 425
 ——— symptoms of, 422
 ——— treatment of, 428
 ——— by aspiration, 429, 430
 ——— Manson's method of, 431
 ——— prognosis of, 434
 ——— by hepatic phlebectomy, 429
 ——— by open operation, 432
 ——— transperitoneal route, 432
 ——— transpleural route, 432
 ——— postoperative, 432
 ——— when discharging through lung, 433
 ——— when rupturing into serous cavity, 434
 ——— enlargement of, in kala-azar, 139
 ——— in malaria, 56, 59, 62
 ——— in hepatic abscess, 420, 423
 ——— in malaria, 56, 62
 ——— in yellow fever, 195
 ——— parasites of, 581
 ——— pus, characters of, 421, 426
 ——— rot, 714
 ——— soup in treatment of sprue, 453
 ——— tropical (see Tropical liver)
 Lizards, 844
 ——— venomous, 613
 Loa loa, 569, 756, 779
 ——— and filariasis, 569
 ——— Calabar swellings and, 571
 ——— characters of, 779
 ——— embryo of, 783
 ——— geographical distribution of, 779
 ——— larva of, 569
 ——— life-history of, 569, 784
 ——— papionis, 779
 Local diseases of problematical nature, 659
 Locke's solution, 145, 675, 865
 Lophocercaria, 736
 Loxotrema ovatum, 713, 719
 ——— characters of, 719
 ——— eggs of, Pl. xxxv, facing p. 874
 ——— habitat and geographical distribution of, 719
 ——— life-history of, 719
 ——— pathogenesis of, 719
 Lugol's solution, 882
 Lung, parasites of, 581
 Lycosa tarentula, 616
 Lymph serotum, 554
 Lymphangitis and elephantoid fever, 550
 Lymphatic trunks, thickened, 553
 ——— varices, cutaneous and deeper, 553
 ——— varix, pathology of, 546
 Lymphocytes, significance of, 861
 Lymphuria, 557
 Lynchia maura, 702
 Lyperosia auctt, 823
 ——— irritans, 826
 Lyperosiops, 823

M

Macacus, 167, 699
 ——— and sleeping sickness inoculations, 116
 ——— cynomolgus, 764
 ——— rhesus, 190, 216

Macacus sinicus, 764
 "Macaw-worm," 617, 804
 "Machoir," 614
 Macrogametes, 700
 Macrogametocytes, 25, 700
 Macrophage, large hyaline, 861
 Madre buba, 488
 Madura foot, 635
 Madurella mycetomi, 639
 ——— tozeuri, 639
 Main-en-griffe, 476
 Mal de caderas, 688
 Mal del pinto, 650
 ——— du coit, 688
 ——— rosso, 346
 Malaria, 1
 ——— acquired immunity and, 9
 ——— æstivo-autumnal, 5
 ——— and anophelines, 19
 ——— and blackwater fever, 44
 ——— differential diagnosis of, 66
 ——— and general paralysis, 21, 32
 ——— and quinine, 69
 ——— artificial infection of anophelines with, 20
 ——— artificially produced in general paralysis, 21, 32
 ——— bilious remittent, diagnosis of, from yellow fever, 67
 ——— treatment of, 83
 ——— blood in, 57
 ——— "brassy bodies" in, 27
 ——— cardiac degeneration in, 57
 ——— cerebral, 83
 ——— complement-deviation test in, 64
 ——— congenital, 22
 ——— convulsive seizures of, 40
 ——— "crescent bodies" in, 13, 27, 28
 ——— diagnosis of, 63, 309
 ——— by blood examination, 63
 ——— by clinical signs, 65
 ——— by patient's history, 65
 ——— by splenic puncture, 65
 ——— by therapeutic action of quinine, 64
 ——— from liver abscess, 66, 428
 ——— from other paroxysmal fevers, 67
 ——— from typhoid and paratyphoid fevers, 67
 ——— from yellow fever, 67
 ——— microscopical, bearing of quinine on, 64
 ——— provocative methods of, 66
 ——— epidemiology and endemology of, 6
 ——— etiology of (see Malaria parasites; Malaria, mosquito and; Malaria infection)
 ——— fever, benign tertian (see Malaria fever, tertian)
 ——— bilious remittent, 67
 ——— treatment of, 83
 ——— clinical forms of, 23
 ——— phenomena of, 29
 ——— delirium in, sudden, 39
 ——— differential diagnosis of, 63
 ——— embolism of cerebral capillaries in, 40
 ——— malignant (see Malaria fever, subtertian)
 ——— periodicity in, 29
 ——— as diagnostic indication, 65
 ——— quartan, 35
 ——— course of, 35
 ——— geographical distribution of, 4
 ——— treatment of, 69
 ——— quotidian, 32, 36

Malaria, hæmoglobin value of corpuscles in, 57

- hæmoglobinæmia in, 61
- heart in, 57
- history of, 1
- hyperpyrexia in, 39, 83
- treatment of, 83
- immunity and, 9
- infection, circumstances favouring, 8
- disturbance of soil and, 8
- endemic and epidemic fluctuations of, 6
- influence of altitude in, 7
- of atmospheric temperature in, 7
- of local conditions in, 6
- of meteorological conditions in, 8
- of water in, 7
- of winds in, 8
- mixed, 32
- possible reservoir of, 22
- time of day and, 8
- kidney in, 57
- leucocytes in, 58
- liver in, 56
- microscopical examination of blood in, 63
- morbid anatomy of, macroscopic, 59
- mosquito and, 1, 22, 813
- natural infection of anophelines with, 19
- parasites, 10
 - abnormal appearances of, 28
 - asexual cycle of, defined, 700
 - benign, 23
 - tertian, 3, 23, 24
 - and G.P.I., 32
 - gametogony in, 24
 - schizogony in, 24
 - characters of, tabulated, 23
 - "crescent bodies" of, 13, 27, 28
 - cultivation of, 29, 865
 - endogenous cycle of, 10, 700
 - exogenous cycle of (*see* Malaria parasites, mosquito cycle of)
 - extracorporeal cycle of (*see* Malaria parasites, mosquito cycle of)
 - "flagellated bodies" of, 12
 - forms of, 23
 - intracorporeal cycle of, 10, 700
 - malignant (*see* Malaria parasites, subtertian)
 - maturation of, 700
 - morphology of, 10
 - mosquito cycle of, 12
 - first stage of, 12
 - second stage of, 15
 - third stage of, 17
 - persistence of, in human body, 25, 26, 28
 - possible latent phase of, 22
 - quartan, 4, 23, 25
 - gametogony in, 26
 - schizogony in, 25
 - sexual cycle of, defined, 700
 - structure of, in human cycle, 10
 - subtertian, 5, 23, 24, 26
 - "crescent bodies" of, 13
 - 27, 28
 - gametogony in, 27
 - schizogony in, 27
 - technical terms used in connexion with, 700

- Malaria parasites, tertian (*see* Malaria parasites, benign tertian)
 ——— transference of, to human host, 19
 ——— transmission of, to foetus, 22
 ——— parasite-index in, 56
 ——— pathology of, 57
 ——— pernicious attacks of, 39, 43
 ——— phagocytosis in, 58
 ——— pigment in, distribution of, 59
 ——— nature and source of, 60
 ——— yellow, 61
 ——— polycholia in, 61
 ——— prognosis of, 68
 ——— prophylaxis of, 87
 ——— anti-mosquito measures, 87
 ——— bonification schemes, 93
 ——— cultivation of trees and plants, 95
 ——— danger from vicinity of natives, 95
 ——— drainage, cultivation, and flooding, 87
 ——— drugs, etc., 98
 ——— education, 99
 ——— fish as larvicides, 92
 ——— killing of adult mosquitoes, 92
 ——— location of dwelling-houses, 94
 ——— mosquito repellents, 96
 ——— mosquito-netting, 95
 ——— mosquito-protected houses, 97
 ——— native experience and, 95
 ——— oil-spraying and oil-burning, 90, 91
 ——— plants as larvicides, 92
 ——— relapse in, influence of meteorological conditions on, 8
 ——— seasonal incidence of, 5
 ——— spleen in, 31, 54, 65
 ——— "spleen-rate" in, 55
 ——— "splenic index" in, 55
 ——— syncopal form of, 41
 ——— theory of blackwater fever, 46
 ——— toxin, acquired tolerance of, 9
 ——— treatment of, 69
 ——— anti-relapse, 74
 ——— by cinchona febrifuge, 75
 ——— by quinine (*see* Quinine in treatment of malaria)
 ——— by salvarsan, 78
 ——— by Warburg's tincture, 75
 ——— general, 84
 ——— prophylactic, 98
 Malarial amblyopia, 39
 ——— cachexia, 53
 ——— pathology of, 54
 ——— treatment of, 84
 ——— coma, 39
 ——— dysentery, 438
 ——— hæmoglobinuria (*see* Blackwater fever)
 ——— injections for general paralysis of insane, 32
 Malignant malarial fever (*see* Malaria fever, subtertian)
 "Malmignatte," 615
 Malta fever (*see* Undulant fever)
 Mambas, 849
 Mammæ, elephantiasis of, 566
 Mannitol-quinine, 80
 Mansonioides africanus, and Filaria bancrofti, 776
 Margaropus bovis, 797
 Marmite in beriberi, 340, 342
 Marmot, and plague, 245
 ——— pouched, of Caucasus, [and] plague, 246
 Marmota flaviventer, 225
 Marris's atropine test, 292
 Mastigophora, 673, 680
 Maurer's clefts, 27, 48
 Mbori, 688
 McKay's method of staining flagellated body, 860
 Measles, rash of, 318
 Medical entomology, 792
 ——— helminthology, 711
 ——— herpetology, 844
 ——— protozoology, 672
 ——— zoology, 670
 Mediterranean fever (*see* Undulant fever)
 ——— yellow fever, 181
 Megaloblasts, significance of, 862
 Megalocytes, significance of, 862
 Meiosis, 673
 Melania gottschei, 721
 ——— libertina, 719, 721
 ——— nodocincta, 727, 731
 ——— obliquegranulosa, 721
 ——— paucicincta, 721
 Melioidosis, 267
 ——— diagnosis of, 268
 ——— etiology of, 267
 ——— symptoms of, 268
 ——— treatment of, 268
 "Melitene" reaction, 273
 Melophagus ovinus, 688
 Mercurochrome 220, in relapsing fever, 179
 ——— in schistosomiasis, 534
 ——— in spotted fever of the Rocky Mountains, 228
 ——— in undulant fever, 279
 Merozoites, 23, 700
 Metagonimus yokogawai, 719
 Metazoa, 672
 Metric and imperial standards, relation between, 889
 Mianeh fever, 167, 175
 Micrococcus melitensis, 269 (footnote)
 Microcyte, significance of, 862
 Microfilaria bancrofti, 535
 ——— characters of, 537, 772
 ——— life of, in mosquito, 542
 ——— non-periodic strains of, 541
 ——— periodicity of, 538, 569, 774
 ——— retirement of, to larger arteries and lungs, 540
 ——— species of mosquito in which it develops, 776
 ——— demarquayi, 535
 ——— diurna, 535, 569, 783
 ——— loa, 535, 569, 783
 ——— distinction of, from mf. bancrofti, 783
 ——— life-history of, 784
 ——— periodicity of, 569
 ——— ozzardi, 535
 ——— perstans, 535, 785
 Microgamete, 12, 14, 700
 Microgametocyte, 25, 700
 Micon, 889
 Micropechis, 852
 Microphage, 861
 Microsporum furfur, 645
 ——— mansoni, 645
 ——— minutissimum, 645
 Microtrombidium akamushi (*see* Trombicula akamushi)
 ——— molestissimum, 794
 ——— wichmanni, 794
 Microtus, 794
 ——— montebelloi, 710
 ——— and infectious jaundice, 181
 ——— and Japanese river fever, 230
 ——— and seven-day fever, 188
 Micrurus, 849, 850, 853
 Midges, 803, 809
 ——— differentiation of, from mosquitoes, 809
 Milk cure of sprue, 450

Milletia sericea, 605
 Miner's anemia (*see* *Ancylostomiasis*)
Miracidium, 711
 Mitigal in treatment of scabies, 793
Mitosis, 673
 Mixed fever, malarial, definition of, 32
Monilia, 633
 — psilosis, 441
Monogenea, 711
Mononuclears, 861
Moogrol, 481
Morbus bengalensis, 388
 Mosquito repellents, 96
 Mosquitoes, 803, 804, 809
 — anatomy of, 805, 806
 — and dengue, 206
 — and filariasis, 542
 — and malaria, 1, 22, 813
 — and yellow fever, 190, 193, 194
 — caging of, 886
 — collecting of, 886
 — differentiation of, from other blood-sucking insects, 809
 — dissection of, 886
 — of head of, 19 (fig.)
 — eggs of, 804, 806
 — geographical range of, 804
 — life-history of, 804
 — migrations of, 806
 — mounting of, 887
 — protection of houses from, 97
 — sections of, celloidin, 888
 — species known to foster *Filaria bancrofti*, 776
 — malaria parasites, 813
 — subfamilies of, 810
 Mosquito-malaria theory, 1
 Mosquito-netting, 95
 Mossy foot, 641
 Mother yaw, 488, 489
 "Mottling, subcuticular," in typhus fever, 221
 Mozambique ulcer, 625
Mucor racemosus, 349
Mucus in faeces, 881
Mugil cephalus, 719
 "Mulberry rash" in typhus fever, 221
Multiceps multiceps, larval form of, 750
Muræna, 613
Murrina, 687
Mus griseiventer, 267
 — jerdoni, and Japanese river fever, 230
 — musculus, 749
 — and plague, 244
 — sylvaticus, 749
Musca domestica, 381, 621, 804, 826
 — as carrier of dysenteric infection, 381
Muscidae, 804, 823
 — blood-sucking, 823
 — non-blood-sucking, 826
Muscle-fibres in faeces, 879
 — significance of, 879
Muscoid flies, 617
 Mwanza outbreak of sleeping sickness, 125
Mycetoma, 635
 — actinomycotic, 638
 — Bouffard's black, 639
 — white, 640
 — Brumpt's white, 639
 — Carter's black, 639
 — classification of, 638
 — etiology of, 638
 — history and geographical distribution of, 635
 — Nicolle's white, 638
 — pathology of, 640
 — Reynier's white, 640

Mycetoma, symptoms of, 635
 — treatment of, 641
 — Vincent's white, 638
Mygale, 616
Myiasis, 617
 — intestinal, 620
 — linearis, 619
 — nasal, aural, and ocular, 617
 — subcutaneous, 617
Myriapoda, 616
 — rossi, and *Filaria bancrofti*, 776

N

Nagana, 686
Nails, ringworm of, 647
Naja, 851
 — lannah, 849
 — morgani, 849
 — naja, 849
 — spp., 848
Nanukayami, 188
 Napier's aldehyde test, 146
 Naso-pharyngeal leishmaniasis, 160
Necator americanus, 589, 590, 756, 760
 — characters of, 761
 — eggs of, 876
 — habitat of, 760
 — life-history of, 762
Nemathelminthes, 711, 754
Nematoda, 754
 — anatomy of, 754
 — development of, direct, 755
 — indirect, 755
 — eggs of, in faeces, 875, and Pl. xxxv, facing p. 874
 — life-history of, 754
 — parasitic in man, classification of, 756
 — pathological effects of, 755
 — preservation of, 886
Neo-salvarsan (see Salvarsan)
Nerium odorum, 605
Nerve leprosy, 473
Neuritis, central, of Jamaica, 345
 Newstead's classification of *Glossina*, 823 (footnote)
 Nicolle and Conseil, and undulant fever, 281
 Nicolle, Novy, and MacNeal (N.N.N.) medium, preparation of, 864
 Nicolle's white mycetoma, 638
 N.N.N. medium, 864
Nocardia tenuis, 654
Nodular dermatitis, 631
 — leprosy, 472
Noguchi-Wenyon medium, preparation of, 864
Nomenclature, zoological rules of, 671
Notechis, 852
 Novarsenobillon for intravenous injection, 666
 Novarsuroil (*see* *Salvarsan*)
Nucleus of protozoan cell, 672
Nyctotherus faba, 708

O

Obermeier, and discovery of *Spironema recurrentis*, 164
Ocular sparganosis, 743
Odan-eki, 181
Oedema (see Epidemic dropsy)
Oesophagostomum apiostomum, 756, 762
 — and formation of intestinal tumours, 755
 — in dysentery, 437
Oestridæ, 804, 832

- Ogmodon, 852
 Oleum gynocardium, 480
 Oligocythæmia in malaria, 57
 Omentopexy for visceral schistosomiasis, 530
 Onchocerca cæcutiens, 573, 787
 ——— volvulus, 572, 573, 756, 786
 ——— and crawl-crawl, 632
 ——— characters of, 573, 786
 ——— eye lesions and, 574
 ——— geographical distribution of, 572, 786
 ——— habitat of, 786
 ——— history of, 572
 ——— life-history of, 787
 Onchocerciasis, human, 572
 Oncomelania, and Eastern schistosomiasis, 531
 ——— formosana, 731, 733
 ——— hupensis, 731, 733
 ——— nosophora, 731, 733
 Oncoerhynchus perryi, 742
 Oöcysts, 17
 Oökinetes, 15, 700
 Operculum, 712
 Ophidia, 844
 "Opilacæo," 126
 Opisthoglypha, 847
 Opisthorchidæ, 713
 Opisthorchis felineus, 713, 717
 ——— eggs of, Pl. xxxv, 4, facing p. 874
 ——— neverca, 718
 ——— viverrini, 718
 Opium poisoning, 606, 608
 Orchitis, filarial, 559
 Oreja de chichleros, 160
 Organelles, 673
 Oriental sore, 151
 ——— age and, 154
 ——— and kala-azar, 151
 ——— diagnosis of, 156
 ——— epidemiology and endemiology of, 152
 ——— etiology of, 152
 ——— generalized non-ulcerating form of, 156
 ——— geographical distribution of, 152
 ——— incubation period of, 154
 ——— lupus-like lesions in, 156
 ——— occupation and, 154
 ——— prophylaxis of, 159
 ——— race and, 154
 ——— seasonal incidence of, 152
 ——— sex and, 154
 ——— social conditions and, 154
 ——— symptoms of, 154
 ——— constitutional, 154
 ——— treatment of, 156
 ——— by carbon-dioxide snow, 159
 ——— by injection of emetine, 159
 ——— of other drugs, 159
 ——— by intravenous tartar emetic, 156
 ——— by ionization, 159
 ——— by tartar-emetic ointment, 158
 ——— by X-rays, 158
 ——— verrucose form of, 156
 Ornithodoros, 164, 795, 797
 ——— lahorensis, 167, 168, 797, 798
 ——— maroccanus, 167, 168
 ——— moubata, 164, 167, 168, 169, 686, 797
 ——— savignyi, 686, 797, 798
 ——— talajé, 167, 168, 797, 798
 ——— and relapsing fever, 164
 ——— tholozani, 167, 168, 797, 799
 ——— venezuelensis, 167, 168, 797, 799
 Ornithodoros venezuelensis, and relapsing fever, 164
 "Oro," 606
 Oroya fever, 233
 ——— and verruga peruana, 233
 ——— etiology of, 233
 ——— geographical distribution of, 233
 ——— history of, 233
 ——— incubation period of, 235
 ——— mortality of, 236
 ——— pathology of, 235
 ——— seasonal incidence of, 235
 ——— symptoms of, 235
 ——— treatment of, 238
 (see also Verruga peruana)
 Os calcis, endemic hypertrophy of, 663
 Oscol stibium, for intramuscular injections in leprosy, 482
 ——— in filariasis, 567
 Oxylax, 768
 Oxyuranus, 851
 Oxyuriasis, 768
 Oxyuridæ, 756
 Oxyuris vermicularis, 767

P

- Pahvant Valley plague, 264
 Palsy, Scott's, 345
 Pangonia rüppellii, 822 (fig.)
 Pani-ghao, 601
 Papataci fever, 210
 Papio cynocephalus, 779
 Parabasal body, 672
 Paragonimiasis, 581
 ——— diagnosis of, 583
 ——— etiology of, 581
 ——— geographical distribution of, 581
 ——— history of, 581
 ——— parasite of, 581
 ——— pathology of, 581
 ——— prophylaxis of, 584
 ——— sputum in, 582
 ——— symptoms of, 582
 ——— treatment of, 584
 Paragonimus compactus, 719
 ——— kellicotti, 721
 ——— ringieri, 581, 719
 ——— characters of, 720
 ——— eggs of, 582, 720, 721, and Pl. xxxv, facing p. 874
 ——— geographical distribution of, 721
 ——— habitat of, 719
 ——— life-history of, 721
 ——— pathogenesis of, 582
 ——— westermanii, 581, 719
 Paramphistomidæ, 713, 733
 Parangi, 486
 ——— pink, 493
 Parasaccharomyces ashfordi, 441
 Parasites, animal, and associated diseases, 511
 ——— intestinal, 587
 ——— eggs of, examination of feces for, 875
 ——— method of concentrating, 876
 ——— of circulatory system, 511
 ——— of liver, 581
 ——— of lung, 581
 ——— of lymphatic system and connective tissue, 535
 ——— of malaria (see Malaria parasites)
 ——— transmission of, 670
 Parasmallpox, 299
 Paratyphoid fevers, diagnosis of enteric from, 293

- Paratyphoid fevers, diagnosis of malaria from, 67
- Paratyphoid-A fever, 283
— diagnosis of rash of, 318
- Paratyphoid-B fever, 283
- Paratyphoid-C fever, 284
- "Parquit," 820
- Patau, 229
- Paullinia pinnata, 605
- Pedetes caffer, 246
- Pediculoides, 793
— ventricosus, 658, 793
- Pediculosis, infection with, 835
— prophylaxis and treatment of, 835
- Pediculus, and relapsing fever, 164
— capitis, 834
— and typhus fever, 219
— corporis, 834
— and typhus fever, 219
— humanus, 164, 167, 168, 834
— and typhus fever, 219
- Pelamis, 848
— platurus, 848
- Pel-Ebstein disease, diagnosis of tropical fevers from, 309
- Pellagra, 346
— age and, 348
— diagnosis of, 356
— of sleeping sickness from, 115
— duration of, 355
— epidemiology and endemology of, 347
— etiology of, 348
— food-deficiency theory of, 350
— infection theory of, 319
— intoxication theory of, 319
— maize theory of, 349, 351
— general description of, 346
— geographical distribution of, 346
— history of, 346
— occupation and, 348
— pathology of, 353
— prophylaxis of, 357
— season and, 347
— sex and, 348
— symptoms of, 353
— treatment of, 356
— typhus, 356
— vitamins and, 350
- Pelletierine tannate in cestode infection, 602
- Pemphigus contagiosus, 631
— leprosus, 475
- Penicillium glaucum, 349
- Pentastomidae, 799
- Pentatrachomonas, 695
- Perca fluviatilis, 742
- Periodicity, filarial, 538, 541, 569
— malarial, 29, 65
- Peripheral neuritis, 345
- Periplaneta americana, as host of Spiroptera neoplastica, 755
— orientalis, 749
- Pernicious attacks in subtertian malaria, 39
- "Persian bug," 798
- Pestis minor, 254
— siderans, 254
- Petrolax, 401
- Pfeiffer's reaction, 366
- Phagedæna, tropical sloughing, 624
- Phagocytosis in malaria, 58
- Phaseolus radiatus, 326
- Phasianus formosanus, 230
- Phialophora verrucosa, 641
- Phlebotomus argentipes, 706, 820
— and transmission of kala-azar, 136
— bionomics of, 820
— dubosequi, 820
- Phlebotomus fever, 210
— diagnosis of, 212, 313
— distribution of, 210
— etiology of, 211
— history of, 210
— incubation period of, 212
— pathology of, 211
— prophylaxis of, 213
— symptoms of, 212
— treatment of, 213
— genus, 211, 689, 809, 817
— differentiation of, from mosquitoes, 809
- lutzi, 161
— major, 137, 820
— minutus, 820
— papatasi, 153, 211, 820
— geographical distribution of, 817
— life-history of, 818
— perniciosus, 820
— perturbans, 820
— possible carrier of Leishmania tropica, 153, 689
— repellents of, 820
— sergenti, 137, 820
— verrucarum, 234
- Phoorsa, 610
- Phthirus pubis, 834
- Physa subopaca, 725
- Physaloptera mordens, 756, 757, 758
- Physalopteridae, 756
- Physopsis africana (see Bullinus africanus)
- Pian, 486
- Pian-bois, 160
- Pica, in ancylostomiasis, 593
- Piedra, 652
- Pigment, malarial, 59
- Piles, internal, 439
- Pinta, 650
— diagnosis of, 652
— etiology of, 650
— geographical distribution of, 650
— symptoms of, 650
— treatment of, 652
- Piophilæ casei, 621
- Piper betel, 608
- "Pipsa" fly, 821
- Piroplasma, 703
- Pit-vipers, 854, 855
- Pityriasis versicolor, 644
- Plague, 239
— age and, 240
— atmospheric temperature and, 240
— bubonic, 252
— mortality of, 255
— diagnosis of, 255
— from post-mortem indications in rats, 256 (footnote)
— distribution of, geographical, 239
— epidemiology and endemology of, 240
— etiology of, 241
— (see also Bacillus pestis)
— experimental, 242
— history of, 239
— in lower animals, 245
— incubation period of, 251
— inoculability of, 242
— isolation of organisms post mortem in, 874
— mortality of, 255
— occupation and, 240
— pathology of, 250
— pneumonic, 255
— mortality of, 255
— prophylaxis of, general, 258
— destruction of, 259
— personal, 260
— Haffkine's, 260
— vermin in, 263

- Plague, quarantine in, 258
 — relapses in, 255
 — rôle of flea in, 247
 — — of marmot and other rodents in, 245
 — — of rat in, 244, 250
 — seasonal incidence of, 249
 — septicæmic, 254
 — sex and, 240
 — symptoms and stages of, 251
 — treatment of, 257
 — — by mercurochrome 220, 257
 — — by serum, 257
 Planorbis boissyi, 518, 522, 729, 731
 — centrimetralis, 727, 731
 — cœnosus, 715
 — corneus var. metidjensis, 727, 731
 — dufourii, 727
 — exustus, 518, 736
 — guadelupensis, 729, 731
 — largillierti, 715
 — neosudanicus, 729, 731
 — nitidella, 715
 — olivaceus, 729, 731
 — pfeifferi, 727, 729, 731
 — schmackeri, 715
 — sudanicus, 729, 731
 Plasmochin (*see* Plasmoquine)
 Plasmodiæ, life cycle of, 699
 Plasmodium, 699
 — characters of, 699
 — cynomolgi, 699
 — falciparum, 17, 18, 22, 23, 26, 27, 699
 — — persistence of, in human body, 28
 — — inui, 699
 — — kochi, 699
 — — life-cycle of, 699
 — — malariae, 25, 699
 — — persistence of, in human body, 26
 — — pitheci, 699
 — — præcox, 1, 699
 — — vivax, 23, 24, 699
 — — persistence of, in human body, 25
 Plasmoquine, 29
 — in blackwater fever, 99
 — in malaria, 76, 98
 Platelets, blood-, 862
 Platyhelminthes, 711
 Plecoglossus altivelis, 719
 Plehn's theories of mechanism of hæmo-
 lysis in blackwater fever, 49
 Plotosus anguillaris, 614
 Pneumo-enteritis, 267
 Pneumonic plague, 255
 Poikilocytosis, 862
 "Pointolite" lamp, 883
 Poisonous fishes, 613
 — foods, 606
 — lizards, 613
 — snakes, 609
 Poisons, animal, 609
 — arrow, 604
 — used for criminal purposes, 605
 — vegetable, 604
 "Polar bodies," 700
 Polycholia in malaria, 61
 Polychromasia, 862
 Polymastigina, 693
 Polymorphonuclear, neutrophile, 861
 Polyneuritis endemica, 321
 — gallinarum, 324
 Polyplax serratus, 265
 — spinulosa, 688
 Polypus, simple, dysentery and, 439
 Ponos, 132
 Porocephalus armillatus, 801
 Porocephalus armillatus characters of, 801
 — — geographical distribution of, 801
 — — life-history of, 802
 — — pathogenesis of, 803
 Postdysenteric constipation, treatment of, 400
 Potamon dehaani, 721, 722
 — obtusipes, 721
 Potassium-antimony tartrate for intra-
 venous injections, 665
 "Potu"-fly, 821
 Premonitory diarrhœa, 367
 Prickly heat, 632
 — — etiology of, 632
 — — treatment of, 634
 Principe, trypanosomiasis-prophylaxis in, 122
 Progressive dilution of serum in agglu-
 tination, 868
 Protein value, biological, 351
 Proteosoma præcox, 699
 Proteroglypha, 847, 848
 Proteus vulgaris, 223
 Protomonadina, 681
 Protopathic sprue, 446
 Protozoa, characters of, 672
 — classification of, 673
 — culture of, technique of, 866
 — in fæces, demonstration of, 881
 — — films for, 882
 Protozoal cysts in fæces, method of
 concentration of, 881
 — dysentery (*see* Dysentery, amœbic)
 Protozoan cell, modes of multiplication
 of, 673
 — — structure of, 672
 Protozoology, medical, 672
 Pseudactinomycosis, 635
 Pseudapistocalamus, 852
 Pseudechis, 852
 Pseudelaps, 851
 Pseudocerastes, 855
 Pseudo-cholera, 267
 Pseudo-parasites in fæces, 881
 Pseudophyllidea, 739
 — anatomy of, 739
 — eggs of, 740
 — larval, occurring in man, 742
 Pseudopodia, 24, 673
 Pseudorashbora parva, 717
 Pseudo-typhus fever, 229
 Psilosis, 440
 — pigmentosa, 346
 Psychodidæ, 803, 817
 Ptomaine poisoning, due to B. aertrycke
 and B. enteritidis, 297
 Puff-adder, 854
 Pulex irritans, 248, 654, 749
 — — and plague, 248
 Pulmonary amœbiasis, 435
 Pulque, 608
 Pulses, as antiscorbutics, preparation of,
 360
 Purru, 486
 Pygidium, 839
 Pyosis mansonii, 631
 Pyralis farinalis, 749
 Pyrexias, tropical, diagnosis of, by sea-
 sonal incidence, 316
 Python regius, 801
 — sebae, 801, 803

Quarantine in cholera, 376
 — in plague, 258
 Quartan fever (*see* Malaria fever, quartan)
 Quartana duplex, 29

Quartana triplex, 30
 Quinidine in malaria, 73
 Quinine abscess, 81
 — amblyopia, 71
 — and plasmoquine, 77
 — derivation of, 69
 — dosage of, 71
 — for intramuscular injections, 666
 — for intravenous injections, 666
 — for pregnant malaria patients, care as to, 71
 — in diagnosis of malaria, 64
 — in prophylaxis of malaria, 98
 — in puerperal state, 71
 — in treatment of heat-hyperpyrexia, 306
 — of malaria, 69
 — — — — — adjuncts to, 74
 — — — — — alkaline modification of, 72
 — — — — — by intramuscular injection, 79
 — — — — — by intravenous injection, 82
 — — — — — by subcutaneous injection, 82
 — — — — — dosage of, 71, 74
 — — — — — excretion of, 72
 — — — — — mode of action of, 76
 — — — — — per os, 69
 — — — — — per rectum, 82
 — — — — — Warburg's tincture of, 75
 — mannitol-, 80
 — salts of, solubility and equivalent value of, 79
 — taste of, methods of disguising, 70
 — theory of blackwater fever, 46
 — toxic effects of,
 Quotidian fever, 32, 36

R

Radiotherapy (*see* X-Ray treatment)
 Rana nigromaculata, 742
 Rand scurvy, 359
 Rashes of fevers in tropics, diagnosis of, 317
 Rat, and infectious jaundice, 183
 — and plague, 244, 259
 — and rat-bite fever, 216
 — leprosy, 469
 — poisons, 259, 263
 — (*see also* Rattus)
 Rat-bite fever, 215
 — — — — — differential diagnosis of, 218
 — — — — — etiology of, 215
 — — — — — geographical distribution of, 215
 — — — — — history of, 215
 — — — — — incubation period of, 216
 — — — — — parasite of, 215, 710
 — — — — — pathology of, 218
 — — — — — symptoms of, 216
 — — — — — treatment of, 218
 Rat-flea, and plague, 248
 — — bionomics of, 250
 Rat-mite, 705
 Rats, plague, species of, description of, 262
 — — — — — post-mortem indications of plague in, 256 (footnote)
 Rattlesnakes, bites of, 611
 Rattus agrarius, and Japanese river fever, 230
 — — alexandrinus, 749
 — — — — — and infectious jaundice, 181
 — — — — — and rat-bite fever, 216
 — — coucha, 246
 — — decumanus, 262, 749

Rattus decumanus, and Japanese river fever, 230
 — — — — — and plague, 244, 260
 — — — — — norvegicus, 262
 — — — — — and Leptospira icterohæmorrhagiae, 181
 — — — — — and plague, 244, 260
 — — — — — and rat-bite fever, 216
 — — — — — and tularæmia, 265
 — — — — — characters of, 262
 — — — — — rattus, 262, 749
 — — — — — alexandrinus, 262
 — — — — — and Leptospira icterohæmorrhagiae, 181
 — — — — — and plague, 244, 260
 — — — — — and rat-bite fever, 216
 — — — — — frugivorus, 262
 — — — — — rufescens, 262
 — — — — — and Japanese river fever, 230
 Ray fungus, 638
 Record syringe, 664
 Rectal irrigation in chronic bacillary dysentery, 398
 Rediæ, 712
 Reduviidæ, 837
 Reedbuck, 104
 Relapsing bacillary dysentery, 387
 — — — — — fever, 164
 — — — — — diagnosis of, 177, 311
 — — — — — Wassermann reaction in, 178
 — — — — — epidemiology and endemiology of, 168
 — — — — — etiology of, 165
 — — — — — fulminating, 176
 — — — — — geographical distribution of, 164
 — — — — — history of, 164
 — — — — — immunity from, 172
 — — — — — incubation period of, 172
 — — — — — mortality of, 177
 — — — — — parasites of, 165
 — — — — — cultivation of, 166
 — — — — — demonstration of, 165
 — — — — — development of, in louse, 170
 — — — — — — — in tick, 170
 — — — — — different strains of, 166, 167
 — — — — — pathology of, 168
 — — — — — prophylaxis of, 179
 — — — — — symptoms common to all forms of, 172
 — — — — — of bilious typhoid type of, 174
 — — — — — of Central African type of, 176
 — — — — — — — and South American type of, 177
 — — — — — of cosmopolitan type of, 172
 — — — — — of Persian type of, 175
 — — — — — table of strains of treponema and related symptoms of, 167
 — — — — — transmission of, 168, 171
 — — — — — treatment of, 178
 Remittent malarial fever, definition of, 32
 Reptilia, 844
 Reticulocyte, 862
 Reynier's white mycetoma, 640
 Rhabdomys pumilio, 246
 Rheumatism, dysenteric, 388
 Rhinopiocephalus, 852
 Rhinocentrus purpureus, 617, 834
 Rhino-pharyngitis, destructive ulcerous, and yaws, 495
 Rhinosporidiosis, 660
 Rhinosporidium seeberi, 660, 661

Rhipicephalus appendiculatus, 704
 — *sanguineus*, 703, 796
Rhizoplast, 673
 Rhodesiense sleeping sickness (*see* Sleeping sickness, *rhodesiense*)
Rhodnius, 837, 839
 — and South American trypanosomiasis, 127, 128
 — *prolixus*, 686, 838, 839
Rhynchelaps, 852
 Rice, polished, and beriberi, 323, 342
Rickettsia bodies, and spotted fever of Rocky Mountains, 225, 226
 — *proWazeki*, and typhus fever, 220
Ringworm of feet, 646
 — of nails, 647
 — *Tokelau*, 648
 — yaws, 492
Rivanol in amoebic dysentery, 418
 Rockefeller Commission, on prophylaxis of ancylostomiasis, 600
 Rocky Mountain fever (*see* Spotted fever)
 Rogers's treatment of cholera, 374
 — of leprosy, 481
 Ross's black spores, 18
 — researches in mosquito-malaria theory, 1, 2
 — thick-film staining method, 857
 Roundworm (*see* *Ascaris lumbricoides*)
 Rubella, rash of, diagnosis of, 318
 Russell's viper, 610, 854

S

Saccobranthus fossilis, 614
 Sahib's disease, 132
 Sakusku fever, 188
 Salek, 151
 Salines, normal or hypertonic, technique of injection of, 667
 "Salisbury" diet in sprue, 454
Salmo umbla, 742
Salvarsan and derivatives, in amoebic dysentery, 416
 — in malaria, 78
 — in Oroya fever, 238
 — in pellagra, 357
 — in rat-bite fever, 218
 — in relapsing fever, 178
 — in typhus fever, 224
 — in verruga peruana, 238
 — in yaws, 502
 — technique of intramuscular injections of, 666
 — intravenous injections of, 666
Sandflea, 654
Sandflies, 803, 817, 820
 — and transmission of kala-azar, 135
 — of phlebotomus fever, 211
 — differentiation of, from mosquitoes, 809
Sandfly fever, 210
Saprosira genus, 708
 — *grandis*, 708
Sarcocystis muris, 706
 — *tenella*, 706
Sarcodina, 674
 — definition of, 673, 674
Sarcophagidae, 804, 827
Sarcopsylla, 655
Sarcopsyllidae, 839
Sarcoptes scabiei, 792
 — characters of, 792
 — habitat of, 792
Sarcoptidae, 792
arcosporidia, 706

"Sasala," 499
 Scabies, prevention and treatment of, 792
 Scarlet fever, rash of, diagnosis of, 318
Scaurus striatus, 749
Schistosoma, genus, 671
 — *haematobium*, 511, 512, 723
 — cercaria stage of, 726
 — characters of, 512, 723, 731
 — eggs of, 512, 724, 731
 — in faeces, 875, and Pl. xxxv, facing p. 874
 — free embryo of, 725
 — geographical distribution of, 723
 — habitat of, 723
 — in dysentery, 437
 — life-history of, 512, 727
 — miracidium of, 725
 — development of, in fresh-water snails, 512
 — nomenclature of, 671
 — snail-hosts of, 727
japonicum, 530, 729
 — cercariae of, 731
 — characters of, 730, 731
 — eggs of, 730
 — in faeces, 875, and Pl. xxxv, facing p. 874
 — geographical distribution of, 730
 — habitat of, 729
 — life-history of, 731
 — miracidium of, 731
 — snail-hosts of, 732
mansoni, 523, 524, 525, 528
 — characters of, 727, 731
 — eggs of, in faeces, 875 and Pl. xxxv, facing p. 874
 — genital system of, 728
 — geographical distribution, 727
 — habitat of, 727
 — life-history of, 728
spindalis, 736
Schistosoma cercariae (*see* Cercariae, schistosome)
 — eggs in faeces, detection of, by Fülleborn's method, 877
Schistosomes, human, differential table of, 731
Schistosomiasis, 511
 — Eastern, 530
 — diagnosis of, 533
 — etiology of, 531
 — history and geographical distribution of, 531
 — pathology of, 531
 — prophylaxis of, 534
 — symptoms of, 532
 — treatment of, 534
 — intestinal, 523
 — complement-deviation in, 526
 — diagnosis of, 526
 — etiology of, 524
 — hepatic cirrhosis and splenomegaly in, 525
 — history and geographical distribution of, 523
 — pathology of, 524
 — prognosis of, 528
 — prophylaxis of, 528
 — sigmoidoscopic examination in, 527
 — symptoms of, 524
 — treatment of, 527
 — mixed infections of, 516
 — of bladder, 511
 — diagnosis of, 517,
 — by cystoscopic examination, 519

- Schistosomiasis of bladder, diagnosis of, from Fairley's reaction, 518
 ———— from intra-dermal reaction, 518
 ———— from presence of eggs in urine, 517
 ———— etiology of, 512
 ———— history and geographical distribution of, 511
 ———— incubation period of, 215
 ———— pathology of, 512
 ———— prognosis of, 519
 ———— prophylaxis of, 521
 ———— symptoms of, 515
 ———— treatment of, 519
 ———— visceral, 528
 ———— diagnosis of, 530
 ———— etiology of, 528
 ———— geographical distribution of, 528
 ———— morbid anatomy and pathology of, 530
 ———— symptoms of, 529
 ———— treatment of, 530
 (see also Schistosoma)
- Schistosomidae, 713, 722
 Schistosomulum, 738
 Schizogony, 24, 25, 29, 672
 Schizonts, 24, 32, 699, 700
 Schizotrypanum cruzi, 624 (see also Trypanosoma cruzi)
 Schuffner's dots, 24
 Scolopendra morsitans, 616
 Scomberomorus caralla, 614
 Scopolamine, 605
 Scorpena, 614
 Scorpions, stings of, 614
 ———— treatment of, 615
 Scott, H. H., and causation of sprue, 441
 ———— and central, neuritis of Jamaica, 345
 Scott's palsy, 345
 "Screen-cloth," 97
 Screw-worm, 830
 ———— infestation, 617
 Scurvy (in the tropics), 358
 ———— diagnosis of, 359
 ———— etiology of, 358
 ———— infantile, 359
 ———— prophylaxis of, 361
 ———— Rand, 359
 ———— symptoms of, 358
 ———— treatment of, 360
 ———— vitamins and, 307, 326, 358
 Sea-snakes, 848
 Segmentina largillierti, 715
 Sepedon, 850
 Septic sore (see Veld sore)
 Septicæmia due to B. coll, 297
 ———— due to B. fæcalis alkaligenes, etc., 296
 Septicæmic plague, 254
 Serules for intravenous injection, 868
 Serum sickness, in bacillary dysentery, 397
 Serum-formalin reaction in kala-azar, 146
 Serum-therapy in bacillary dysentery, 396
 ———— in infectious jaundice, 187
 ———— in Japanese river fever, 232
 ———— in plague, 257
 ———— in snake-bite, 612
 ———— in typhus fever, 224
 ———— in undulant fever, 279
 ———— in veld sore, 629
 Sesarma dehaani, 721
 Seven-day fever, 188, 205
 ———— diagnosis of, 189, 313
 ———— differential, 189
 ———— etiology of, 188
 ———— geographical distribution of, 188
 Seven-day fever, history of, 188
 ———— incubation period of, 189
 ———— symptoms of, 189
 ———— treatment of, 189
 Sheep-ked, 688
 Shiga and discovery of Bacillus dysenteriae, 382
 Shimamushi, 228
 Ship beriberi, 322
 Shueki, 188
 Siderosis in malarial cachexia, 56
 Simia satyrus, 699
 "Simple continued fever," 188
 Simuliidæ, 803, 820
 Simulium, 820
 ———— damnosum, 573, 787, 821
 ———— geographical distribution of, 821
 ———— indicum, 821
 ———— life-history of, 821
 ———— reptans, 821
 ———— vittatum, 821
 Sinton's alkaline quinine treatment in malaria, 72
 ———— method of cultivation of malaria parasite, 866
 Siphonaptera, characters of, 839
 Siriasis, 303
 Sirkari disease, 132
 Sisturus, 855
 Sitatunga, 104, 684, 687
 Skin diseases, bacterial, 624
 ———— fungous, 632
 ———— non-specific, 623
 ———— of animal origin, 654
 Sleeping sickness, African, 101
 ———— history of, 101
 ———— discovery of cause of, 101
 ———— gambiense, 101
 ———— complications of, 113
 ———— diagnosis of, 114, 312
 ———— by animal inoculation, 116
 ———— by blood examination, 114
 ———— by gland puncture, 116
 ———— by lumbar puncture, 116
 ———— etiology of, 101, 124
 ———— geographical distribution of, 101
 ———— immunity from, 114
 ———— incubation period of, 107
 ———— "Kerandel's symptom" in, 108
 ———— mortality of, 114
 ———— pathology of, 105
 ———— prophylaxis of, 121
 ———— rash in, 109
 ———— reservoir-hosts in, 104
 ———— role of tsetse-fly in, 103
 ———— symptoms of, 107
 ———— terminal stage of, 111
 ———— transmission of, 103
 ———— cyclical, 103
 ———— mechanical, 104
 ———— treatment of, 116
 ———— rhodesiense, 123
 ———— diagnosis of, 125
 ———— etiology of, 124
 ———— geographical distribution of, 124
 ———— Mwanza outbreak of, 125
 ———— prophylaxis of, 126
 ———— symptoms of, 125
 ———— treatment of, 125
 (see also Trypanosomiasis South American)
- Slides, cleaning, 857
 Smallpox in tropics, 299

- Smallpox, rash of, 299
 Smears, staining for spirochaetes in, 885
 Snake, coral, 853
 ——— poisons, 609
 Snake-bite, 609
 ——— colubrine, symptoms of, 609
 ——— treatment of, 611
 ——— serum, 612
 ——— viperine, symptoms of, 610
 Snakes, 844
 ——— bibliography of works on, 856
 ——— classification of, 844
 ——— families of, synopsis of, 846
 ——— identification of, 845
 ——— locomotion of, 845
 ——— poison apparatus of, 844
 ——— synopsis of, 846
 ——— venomous, synopsis of, 844
 Soaps in faeces, 880
 Sodium gynocardate in leprosy, 481
 ——— morrhuate in leprosy, 482
 Sodium-antimony tartrate for intravenous injections, 665
 Sodoku, 215
 Sokosha, 215
 Sonne's bacillus, 383
 Sore feet of coolies, 601
 Souma, 687
 South American trypanosomiasis (*see* Trypanosomiasis, South American)
 Sparganosis, ocular, 743
 Sparganum mansoni, 602, 742,
 ——— proliferum, 602, 743
 Speke's antelope, 105
 Sperophilus guttatus, 246
 Sphyræna barracuda, 614
 Spiders, stings of, 615
 Spirillum fever, 164
 ——— laverani, 216
 ——— minus (morsus-muris), 215, 710
 ——— muris, 216
 Spirochæta eurygyrata, 438,
 ——— genus, 708
 ——— laverani, 710
 ——— morsus-muris (*see* Spirillum minus)
 ——— muris, 710
 ——— pallida (*see* Treponema pallidum)
 ——— plicatilis, 708
 Spirochaetes, 708
 ——— detection of, by dark-ground illumination, 883
 ——— division of, into genera, 708
 ——— schema of different forms of, 709 (fig.)
 Spirochaetosis icterohæmorrhagica (*see* Infectious jaundice)
 ——— of fowls and geese, 709
 Spiroplasma, nomenclature of, 164
 Spiroptera neoplastica, and formation of gastric carcinoma, 755
 Spleen, amœbic abscess of, 435
 ——— enlargement of, in blackwater fever, 49, 51
 ——— in enteric fevers, 290
 ——— in infectious jaundice, 185
 ——— in malaria, 31, 54, 59
 ——— in malarial cachexia, 54
 ——— treatment of, 84
 ——— in relapsing fever, 158, 173, 176
 ——— in spotted fever of Rocky Mountains, 227
 ——— in trypanosomiasis, 111
 ——— puncture in kala-azar, 144
 ——— rupture of, in malarial cachexia, 55
 Splenic index in malarial cachexia, 55
 Splenomegaly and hepatic cirrhosis in Northern Nyasaland, 525
 ——— Egyptian (*see* Schistosomiasis, visceral)
 Splenomegaly, tropical (*see* Kala-azar)
 Sporocysts, 696, 712
 Sporogony, 700
 Sporotrichosis, 643
 Sporotrichum beurmanni, 643
 Sporozoa, 674, 696
 Sporozoites, 17, 18, 699
 Spotted fever (of Rocky Mountains), 224
 ——— complications of, 228
 ——— diagnosis of, 228
 ——— of rash of, 319
 ——— etiology of, 225
 ——— geographical distribution of, 225
 ——— history of, 225
 ——— mortality of, 226
 ——— pathology of, 226
 ——— prophylaxis of, 228
 ——— seasonal prevalence of, 226
 ——— symptoms of, 227
 ——— treatment of, 228
 Sprue, 440
 ——— anemia in, 445
 ——— complications of, treatment of, 459
 ——— constipation in, treatment of, 452
 ——— course of, 446
 ——— diagnosis of, 448
 ——— diarrhœa in, 445
 ——— dietary recommended in, 455, 458
 ——— dyspepsia in, 445
 ——— epidemiology and endemiology of, 440
 ——— etiology of, 441
 ——— calcium-deficiency theory, 441
 ——— food-deficiency theory, 441
 ——— yeast theory, 441
 ——— geographical distribution of, 440
 ——— history of, 446
 ——— incomplete, 448
 ——— gastric cases of, 448
 ——— intestinal cases of, 448
 ——— without diarrhœa, 448
 ——— intestinal atrophy from, 448
 ——— latency of, 448
 ——— mouth lesions in, 444
 ——— pathology of, 441
 ——— prognosis of, 449
 ——— protopathic, 446
 ——— secondary to acute entero-colitis, 447
 ——— to dysentery, 447
 ——— symptoms of, 443
 ——— terminations of, 446
 ——— threatened relapses in, 451
 ——— treatment of, 449
 ——— by blood transfusion, 457
 ——— by chromosantonin, 457
 ——— by drugs, 456, 457
 ——— by fruit, 452
 ——— by liver soup, 453
 ——— by meat and warm-water diet, 454
 ——— by meat-juice and underdone meat, 453
 ——— by milk, 450
 ——— by nutrient enemata or suppositories, 454
 ——— climatic, 456
 ——— general, 456
 ——— in convalescent stage, 458
 ——— Scott's, 456
 ——— types of, 446
 "Squatting test" in beriberi, 338
 Stable-fly, 804
 Stained blood-films, 885
 Stanton's disease, 267
 Staphylococcus pyrogenes albus, 629
 ——— aureus, 629
 Starch granules in faeces, 879
 Stegomyia, 814
 ——— albopictus, 816
 ——— calopus, (*see* Aedes argenteus)

- Stegomyia fasciata* (see *Aedes argenteus*)
 ——— *pseudoscutellaris*, 816
 ——— and filariasis, 542, 775, 776
 ——— *scutellaris*, 816
 ——— *variegatus*, 816
Stenocephalus agilis, 691
Sterigmatocystis nidulans, 638
 Sternberg's mixture, composition of, 202
Stibosan, 148
Stomoxys, 804, 823, 825
 ——— *calcitrans*, 265, 825
Stovarsol in amoebiasis, 417
 ——— in malaria, 78
 ——— in relapsing fever, 178
 ——— in tropical sore, 159
Streptococcus pyogenes, 629
Strongylidae, 756
Strongyloides stercoralis, 756, 765
 ——— characters of, 765
 ——— eggs of, 765
 ——— larval forms of, 766
 ——— life-history of, 765, 766
 ——— pathogenesis of, and treatment, 767
Strophanthus, 604
Strychnos, as source of arrow poisons, 604, 605
 ——— *ovalifolius*, 604
 Subintrans malarial fever, 36
 Subtertian malarial fever (see Malaria fever, subtertian)
Sulphostab, 178
 "Sun disease," 348
 Sunstroke, 307
 Sun-traumatism, 307
Superbin, 605
 Suprarenal glands in subtertian malaria, 62
Surra, 687
Synanceia, 614
 Syncopal subtertian malaria, 41
 Syngamy, 670, 700
 Synkaryon, 696
 Synovitis, filarial, 559
Syntonosphyrum glossinæ, 123
 Syphilis, diagnosis of yaws from, 501
 Syringe and needles for injections, 664
Syringomyelia, diagnosis of leprosy from, 478
- T
- T.A.B. (triple vaccine), 295
Tabanidae, 803, 821
Tabanus diteniatus, 688
 ——— *ustus*, 822 (Fig. 342)
Tabardillo, 219
Tænia africana, 747
 ——— *bremneri*, 747
 ——— *confusa*, 747
 ——— *hominis*, 747
 ——— *lophosoma*, 747
 ——— *multiceps*, larval form of, 750
 ——— *nana*, 747
 ——— *philippina*, 747
 ——— *saginata*, 601, 744, 745, 747
 ——— characters of, 747
 ——— eggs of, in faeces, 876, and Pl. xxxv, facing p. 874
 ——— geographical distribution of, 747
 ——— habitat of, 747
 ——— larval form of, 750
 ——— life-history and pathogenesis of, 747
 ——— varieties of, 747
 ——— *solium*, 601, 745
 ——— characters of, 745
Tænia solium, eggs of, in faeces, 786, and Pl. xxxv, facing p. 874
 ——— geographical distribution of, 745
 ——— habitat of, 745
 ——— larval form of, 750
 ——— life-history and pathogenesis of, 746
Tæniidae, 745
Tæniorhynchus africanus, and Filaria bancrofti, 776
 Tallquist's method of hæmoglobin estimation, 864
 Talma-Morison operation in visceral schistosomiasis, 530
 Tanganyika Territory, sleeping sickness in, 125
 Tapeworms (see Cestodes)
 Tarabagan, and plague, 245
Taraktogenos kurzii, 480
Tarantula spider, 616
Tarsonemidae, 793
 Tartar emetic (see Antimony)
Taterona lobengulæ, 246
Tatusia novemcincta, 686
 ——— and South American typanosomiasis, 131
 Telemann's method of finding eggs in intestinal schistosomiasis, 526
Tenebrio mollitor, 749
Ternidens deminutus, 756, 764
 ——— characters of, 764
 ——— geographical distribution of, 764
 ——— habitat of, 764
 Tertian fever (see Malaria fever, tertian)
 Tetrachlorethylene in ancylostomiasis, 598
Tetratrichomonas, 695
Tetrodon, 614
 ——— *hispidus*, 614
Thalassophis, 848
Thalassophryne, 614
Theileria, 704
 ——— *parva*, 234, 703
 ——— *tsutsugamushi*, 230
Thelazia callipoda, 756
 Thermic fever, 303
Thevetia ahoal, 605
 ——— *neriifolia*, 605
Thevetin, 605
Thevetosin, 605
 Thoma-Zeiss hæmocytometer, 861, 863
Thomomys bottæ bottæ, 265
 Threadworm (see *Enterobius vermicularis*)
 Three-day fever, 210
Thymallus vulgaris, 742
 Thymol in ancylostomiasis, 596
 Tick, development of parasite of relapsing fever in, 169
 ——— fever, 164, 167, 168, 176
 ——— paralysis, 226 (footnote)
 Ticks, characters of, 795
 ——— life-history of, 796
 ——— (see also *Ixodidae*)
 "Tiger mosquito," 814
 Timbolin, 605
Tinca tinca, 718
Tinea cruris (see Dhobie's itch)
 ——— *imbricata*, 648
 ——— *unguim*, 647
 "Tiqui-tiqui," in beriberi, 341
 Tokelau ringworm, 648
 Torcel, 834
Toxascaris canis, 756
Toxicocalamus, 852
Trachinus, 614
 Transfusion in blackwater fever, 86
 ——— intravenous, technique of, 668
 Tree-cobras, 849
 Trematoda, 711

- Trematoda, anatomy of, 713
 ——— key to terminology of, 715 (foot-note)
 ——— characters of, 711, 713
 ——— eggs of, in faeces, 875, and Pl. xxxv
 ——— life-history of, 711
 ——— parasitic in man, 713
 ——— preservation of, 885
 ——— reproductive system of, 711
- Treponema, 166, 708
 ——— anserinum, 709
 ——— berberum, 167
 ——— carteri, 167
 ——— dentium, 709, 885
 ——— duttoni, 165, 167, 709
 ——— eurygyratum, 709
 ——— gallinarum, 709, 799
 ——— gracile, 709
 ——— hispanicum, 167
 ——— neotropicalis, 167
 ——— novyi, 167
 ——— obermeieri (see *Treponema recurrentis*)
 ——— of relapsing fever, table of strains of, and related symptoms, 167
 ——— pallidum, 487
 ——— pallidum, 487, 708, 709
 ——— persicum, 167, 168, 709, 798
 ——— pertenue, 486, 487, 709
 ——— ——— and *T. pallidum*, 487
 ——— ——— cultivation of, 487
 ——— ——— demonstration of, 487
 ——— ——— morphology of, 487
 ——— recurrentis, 164, 167, 171 (fig.), 709
 ——— ——— characters of, 165
 ——— ——— cultivation of, 166
 ——— ——— demonstration of, 165
 ——— ——— different strains of, 167
 ——— refringens, 709
 ——— schaudinni, 625, 709
 ——— systematic position of, 166
 ——— venezuelense, 165, 167
 ——— ——— man the chief reservoir of, 172
 ——— ——— vincenti, 709
- Triatoma, 837
 ——— chagasi, 837
 ——— dimidiata, 686, 838
 ——— ——— var. *maculipennis*, 686
 ——— geniculata, 838
 ——— ——— and South American trypanosomiasis, 131
 ——— infestans, 686, 838
 ——— megista, 127, 131, 682, 686, 837
 ——— ——— and South American trypanosomiasis, 126, 127, 131
 ——— protracta, 686, 838
 ——— rubrofasciata, 686, 837, 838
 ——— sanguisuga, 686, 838
 ——— sordida, 686, 838
 ——— vitticeps, 686, 838
- Tribondeau's hæmatoxylin test, 861
- Trichinella spiralis, 756, 770
 ——— characters of, 770
 ——— diagnosis of, 771
 ——— geographical distribution of, 770
 ——— habitat of, 770
 ——— life-history of, 770
 ——— pathogenesis of, 771
 ——— prophylaxis against, 772
- Trichinelliasis, 711
- Trichinellidæ, 756
- Trichinosis, 772
- Trichocephalus dispar, 768
- Trichodectes canis, 750
- Trichomonas buccalis, 694
 ——— caviæ, 694
 ——— hominis, 693
 ——— intestinalis, 483
 ——— vaginalis, 694
- "Trichomycose nodulaire," 653
- Trichomycosis, 653
 ——— nodosa, 653
- Trichonocardiasis, 653
- Trichosporosis, 652
- Trichosporum giganteum, 653
- Trichostongylus colubriformis, 756, 764, 765
- Trichuridæ, 756
- Trichuris trichiura, 756, 768
 ——— characters of, 768
 ——— eggs of, in faeces, 875, and Pl. xxxv, facing p. 874
 ——— life-history and pathogenesis of, 768
- Trimeresurus, 855
 ——— bites of, 611
- Tritrichomonas, 695
- Trombicula akamushi, 794
 ——— and Japanese river fever, 229, 230
 ——— coarctata, 229
 ——— deliensis, 229, 794
 ——— schuffneri, 230, 794
- Trombididæ, 793
- Trophozoites, 23, 24, 700
- Tropical diarrhoea, 440
 ——— liver, 461
 ——— ——— causes of, 461
 ——— ——— treatment of, 462
 ——— sloughing phagedæna, 624
 ——— ——— diagnosis of, 626
 ——— ——— etiology of, 625
 ——— ——— geographical distribution of, 624
 ——— ——— symptoms of, 625
 ——— ——— treatment of, 626
 ——— sore, 151
 ——— splenomegaly, 132
- Tropidochis, 852
- Trutta lacustris, 742
 ——— vulgaris, 742
- Trypanosoma, 681, 691
 ——— bovis, 687
 ——— brucei, 120, 124, 682, 686
 ——— capræ, 687
 ——— cazalboui, 687
 ——— congolense, 114, 682, 687
 ——— cruzi, 126, 131, 684, 685, 686, 839
 ——— ——— transmission of, 127
 ——— dimorphon, 687
 ——— equinum, 687, 688
 ——— equiperdum, 681, 688
 ——— escomeli, 684
 ——— evansi, 682, 687
 ——— gambiense, 101, 103, 104, 120, 123, 124, 682, 683
 ——— hippicum, 687
 ——— lewisi, 688
 ——— melophagium, 682, 688
 ——— nanum, 687
 ——— nigeriense, 683
 ——— pecorum, 687
 ——— rhodesiense, 120, 121, 124, 125, 126, 682, 684
 ——— rougeti, 688
 ——— simia, 687
 ——— theileri, 682, 688
 ——— uniforme, 687
 ——— vivax, 114, 682, 683, 687
- Trypanosomes, 681
 ——— culture of, 682
 ——— methods of development of, 682
 ——— ——— of transmission of, 681
 ——— of animals resembling those of man, 686
 ——— structure of, 102, 681
- Trypanosomiasis, human (see Sleeping sickness, gambiense; Sleeping sickness, rhodesiense; Trypanosomiasis, South American)

Trypanosomiasis, South American, 126
 ———— diagnosis of, 130, 312
 ———— etiology of, 127
 ———— geographical distribution of, 127
 ———— history of, 126
 ———— pathology of, 128
 ———— prophylaxis of, 131
 ———— symptoms of, 129
 ———— transmission of, 127
 ———— treatment of, 131
 Tryparsamide in gambiense sleeping sickness, 117, 121
 Tsetse-flies (*see* Glossina; Glossinæ)
 Tautugamushi, 228
 Tuberculosis, diagnosis of tropical fevers from, 309
 Tuberculous ulceration of bowel, dysentery and, 439
 Tularemiæ, 264
 ———— diagnosis of, 266
 ———— epidemiology and endemiology of, 264
 ———— etiology of, 264
 ———— history and geographical distribution of, 264
 ———— pathology of, 265
 ———— prophylaxis of, 266
 ———— symptoms of, 265
 ———— treatment of, 266
 Tumbu-fly, 618
 Tumour - formation, *Æsophagostomum* apiostomum and, 755
 Tunga penetrans, 654
 Tungidæ, 839
 Tunnel disease (*see* Ancylostomiasis)
 Turnix taigoon, 230
 Typhlopidae, 846
 Typhoid fever (*see* Enteric fevers)
 ———— remittent fever, 38
 Typhus exanthematicus, 219
 ———— fever (in the tropics), 219
 ———— diagnosis of, 222, 315
 ———— by Weil-Felix reaction, 223
 ———— etiology of, 219
 ———— geographical distribution of, 219
 ———— incubation period of, 220
 ———— pathology of, 220
 ———— prophylaxis of, 224
 ———— rash of, 317
 ———— symptoms of, 220
 ———— treatment of, 223
 ———— by serum, 224
 ———— ictroides, 190
 ———— Indian tick, 224
 Tyroglyphidae, 793
 Tyroglyphus, 658

U

Ulcerating dermatitis, 631
 ———— granuloma of pudenda, 505
 ———— diagnosis of, 508
 ———— etiology of, 505
 ———— geographical distribution of, 505
 ———— incubation period of, 506
 ———— parasitic elements in, 505
 ———— pathology of, 505
 ———— prophylaxis of, 510
 ———— symptoms of, 506
 ———— treatment of, 509
 ———— by a n t i m o n y compounds, 509
 ———— by X-rays, 509, 510
 Ulcus tropicum (*see* Tropical sloughing phagedæna)

Ultracalamus, 852
 Uncinariasis, 589
 Undulant fever, 269
 ———— age and, 270
 ———— agglutination in, 274, 873
 ———— complications and sequelæ of, 277
 ———— diagnosis of, 273, 314
 ———— hæmoculture and, 273
 ———— "melitene" reaction in, 273
 ———— diet in, 279
 ———— duration of, 277
 ———— epidemiology of, 269
 ———— cheese and, 271
 ———— goat's milk and, 270
 ———— local causes of, 270
 ———— manure and, 271
 ———— milk and, 270
 ———— mode of infection in, 270
 ———— season and, 270
 ———— social conditions and, 270
 ———— etiology of, 271
 ———— history and geographical distribution of, 269
 ———— immunity from, 278
 ———— incidence of, in Army and Navy, 269
 ———— incubation period of, 274
 ———— paramelitensis group of cases of, 271
 ———— pathology of, 274
 ———— prognosis of, 278
 ———— prophylaxis of, 280
 ———— by inoculation, 281
 ———— symptoms of, 274
 ———— treatment of, 278
 ———— by injection of metallic compounds, 279
 ———— by serum, 279
 ———— by vaccines, 279
 ———— diet in, 279
 ———— types of, 277
 Uragoya granatensis, 413 (footnote)
 Urea stibamine, 149
 Urechites suberecta, 605
 Urechitin, 605
 Urechitoxin, 605
 Urine, chylous, physical characters of, 557
 ———— examination, spectroscopic, 882
 ———— in ague fit, 31
 ———— in blackwater fever, 51
 Uropeltidæ, 847
 Uta, 160

V

Vaccine prophylaxis (*see* Inoculation prophylactic)
 Vaccine-therapy in enteric fevers, 295
 ———— in filariasis, 567
 ———— in undulant fever, 279
 Vacuoles, contractile, of protozoa, 673
 Varices, lymphatic, cutaneous and deeper, 553
 Varicose groin-glands, 551
 ———— diagnosis of, 551
 ———— treatment of, 552
 Vegetable poisons, 604
 Veld sore, 627
 ———— etiology of, 627
 ———— geographical distribution of, 627
 ———— prophylaxis of, 629
 ———— symptoms of, 627
 ———— treatment of, 629
 Velvet mites, 793

- Ver du Cayor, 618, 831
 — macaque, 617, 833
 Venules for blood-examination, 867
 Vermicule, travelling, 15
 "Vermijelli," 841
 Verruga peruana, 233, 236
 — and Oroya fever, 233
 — diagnosis of, 238
 — etiology of, 236
 — incubation period of, 237
 — mortality of, 238
 — pathology of, 236
 — symptoms of, 237
 — treatment of, 238
 Vibrio, cholera (*see* Comma bacillus)
 Vicia sativa, 606
 Vicine, 606
 Vincent's white mycetoma, 638
 Viper, 853
 Vipera, 854, 855
 — russelli, 610, 854
 Viperidae, 847, 853
 Viperinae, 610, 854
 — African, synopsis of, 854
 — European and Asiatic, synopsis of, 854
 Vitamins, and beriberi, 326
 — and infantile biliary cirrhosis, 463
 — and pellagra, 350
 Vitiligo, 623
 — diagnosis of leprosy from, 478
 Vlemnick's solution, 645
 Volutin, 879
 Vomiting sickness of Jamaica, 606
 "Von Heyden 471," 148, 509
 — 693," 149
 Vulva, elephantiasis of, 566

W

- Wagner-Jauregg, and treatment of general paralysis of insane by malarial injections, 32
 Walterinnesia, 850
 Wanganga, 551
 War oedema, 327
 Warburg's tincture, 75
 Wassermann reaction, in leprosy, 479
 — (footnote)
 — in malaria, 64
 — in relapsing fever, 178
 — in yaws, 492
 Water itch, 601
 — pox, 601
 — sores, 601
 Waterbuck, 104
 Watsonius watsoni, 735
 Weil-Felix reaction in typhus fever, 222, 223, 224,
 — Well's disease (*see* Infectious jaundice)
 West Indian modified smallpox, 299
 "Wet beriberi," 329
 Whipworm (*see* Trichuris trichiura)
 Widal reaction (*see* Agglutination)
 Wohlfahrtia magnifica, 617, 827
 Woodchuck, 225

X

- X 19 (*Proteus vulgaris*), 223
 Xanthoma tuberosum multiplex, 143
 Xenopeltidae, 847
 Xenopsylla, 839, 842
 — astia, 250, 840, 843
 — braziliensis, 250, 843

- Xenopsylla cheopis, 248, 250, 688, 749, 841,
 — 843
 — eridos, 246
 Xiphidio-cercariae, 736
 X-Ray treatment of blastomycosis, 644
 — of oriental sore, 158
 — of ulcerating granuloma of
 — pudenda, 510

Y

- Yangona, 608
 Yatren in treatment of amoebic dysentery,
 — 417, 418
 — of ascariasis, 588
 — of bacillary dysentery, 396,
 — 400
 Yaws, 486
 — age and, 487
 — and goundou, relation between, 497
 — bone lesions in, 498
 — contagion and, 486
 — "crab," 493
 — daughter-yaw in, 489
 — diagnosis of, 501
 — duration and recurrences of, 500
 — epidemiology and endemiology of,
 — 486
 — eruption of, 489
 — etiology of, 487
 — gangosa and, 495
 — general health in, 500
 — geographical distribution of, 486
 — gland-enlargement in, 492
 — foot lesions in, 493
 — hand lesions in, 493
 — heredity and, 486
 — immunity from, 500
 — incubation period of, 488
 — juxta-articular nodules in, 499
 — late manifestations of, 501
 — mortality of, 501
 — mother-yaw in, 488, 489
 — pathology of, 487
 — prophylaxis of, 504
 — ringworm, 492
 — skin lesions in, 499
 — stages of, primary, 488
 — — secondary, 488
 — — tertiary, 492
 — symptoms of, 488
 — synovitis in, 499
 — syphilis and, 501
 — treatment of, 502
 — — by bismuth compounds, 503
 — — by salvarsan and derivatives,
 — — 503
 — — treponema of, 486, 487
 Yeast theory of sprue, 441
 Yellow fever, 190
 — black vomit in, 198
 — diagnosis of, 199, 313
 — — from dengue, 200
 — — of malaria from, 67
 — endemicity of, conditions
 — — favouring, 192
 — epidemiology of, 191
 — etiology of, 193
 — geographical distribution of,
 — — 191
 — history of, 190
 — immunity from, 192
 — incubation period of, 192, 195
 — mortality of, 200
 — pathology of, 194
 — period of calm in, 199
 — — of reaction in, 199
 — prognosis of, 200

Yellow fever, prophylaxis of, 202
 — — — — by inoculation, 204
 — — — — by sanitary measures, 202
 — — — — race and, 192
 — — — — symptoms of, 195
 — — — — black vomit in, 198
 — — — — treatment of, 201
 — — — — Sternberg, 202
 — — — — virus of, 193
 "Yellows," 182
 Yemen ulcer, 625
 Yokogawa's fluke (*see* *Loxotrema ovatum*)
 Yorke's autolytic reaction, 50
 — method of concentration of protozoal
 cysts in fæces, 881

Z

Zammit's test, 281
 Zein, pellagra and, 351
 Zeist theory of pellagra, 349
 Zoomastigina (*see* Flagellata; Hæmoflagel-
 lata)
 Zoological nomenclature, rules of, 671
 Zoology, medical, 670
 — — — entomology, 792
 — — — helminthology, 711
 — — — herpetology, 844
 — — — protozoology, 672
 Zygotes, 15, 700

*Made and Printed in Great Britain by
The Greycaine Book Manufacturing Company Limited,
Watford.
[50.1128*

